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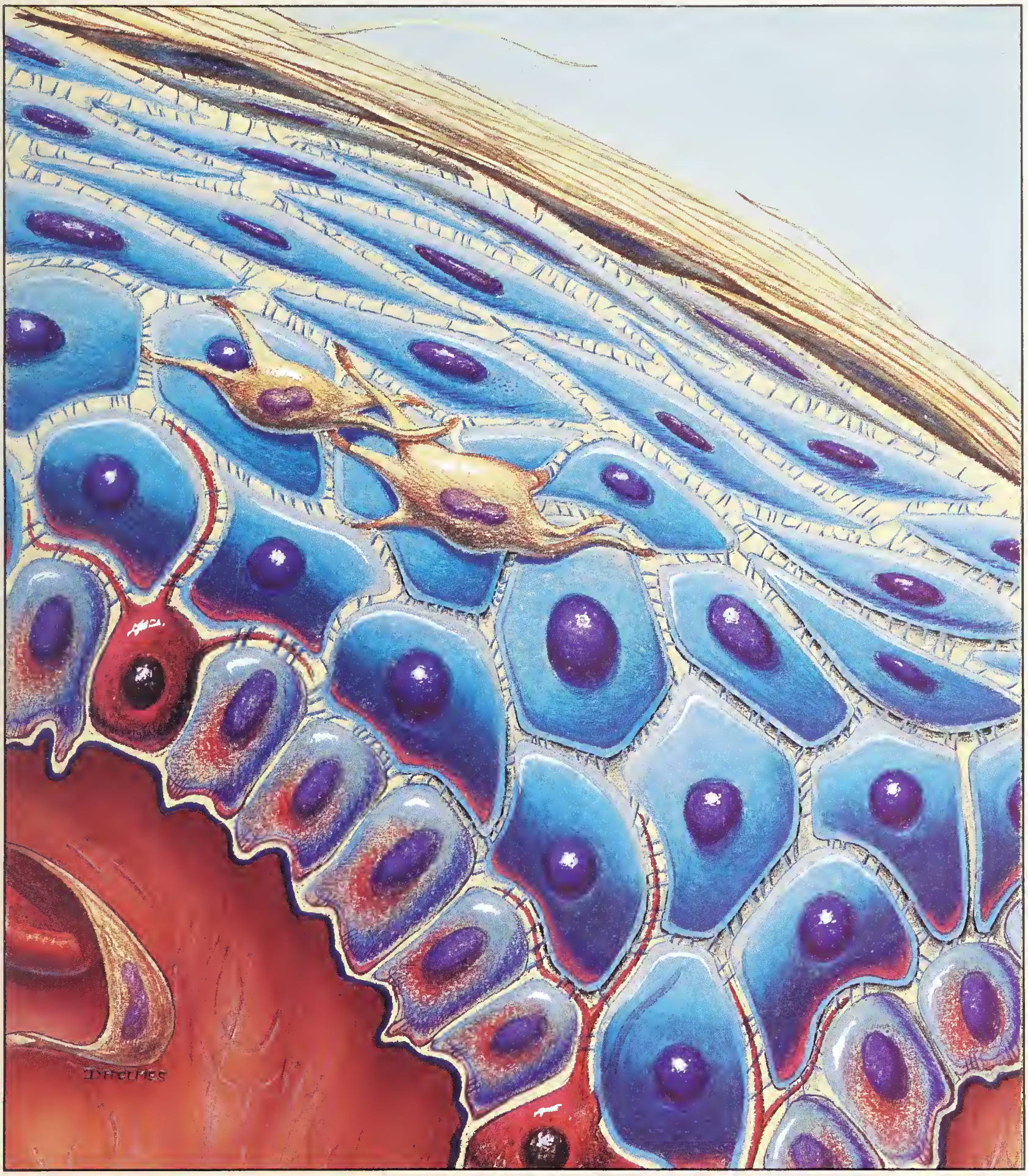

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- Keratinocyte Cytokines
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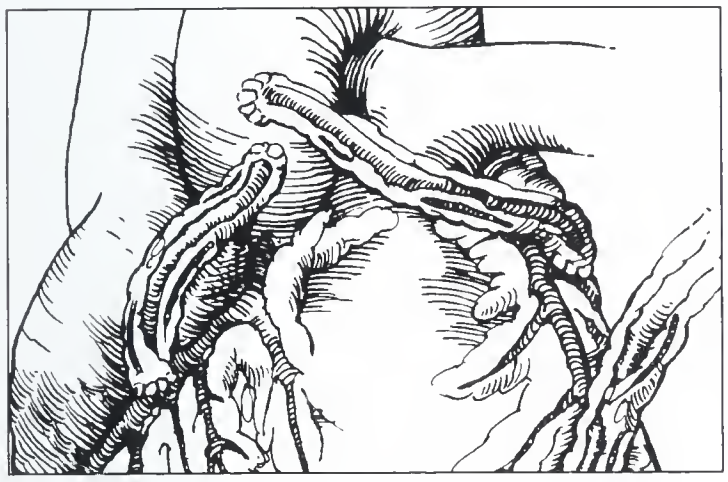

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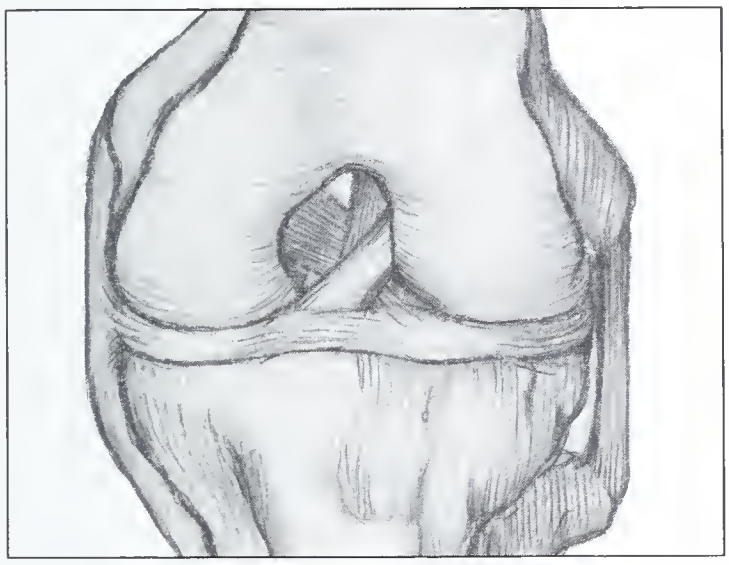

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Front cover illustration by Dustin Holmes, Department of Biomedical Communications, University of Toronto.

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Editorial

Dear Readers,

This publication represents the final issue of the 72nd edition of the U of T Medical Journal. Over the year we have had many submissions from both students and physicians alike, with 17 original papers ultimately being published. In retrospect, we are very pleased with the variety of subject areas in which we were able to publish high quality articles. This issue is no exception. Our cover article admirably summarizes the diversity of keratinocyte cytokines now known. In the article on hereditary stomatocytosis you will read about the first case of its kind ever described in Canada. A recent topic of preoccupation in the national news (and at Daffydil) is explored in the article on necrotizing fasciitis. The articles on coronary artery bypass surgery and MRI imaging of the olivary nucleus will also appeal to a wide audience. It has been awhile since the Journal has published an article with a cut out section; we hope some of our readers will find the cut away in the breast examination article particularly useful.

The focus of the *News and Views* section is the developing Academy structure at the U of T. The three Book Reviews range from light-hearted to academic, hopefully embracing the interests of all. The *Quick Diagnosis* section has been generating enormous community interest and we are sure that this issue's highlighting of infectious diseases is sure to maintain the momentum.

Publishing the Journal is an enormous undertaking, and we would like to acknowledge the help and support we received throughout the year. Thanks to our Associate Editors John Lamensa and Angela Luong, and the entire editorial staff who read and provided comments on all articles received, published or not. Also thanks to our Section Editors: Danyal Ibrahim, D'Arcy Little, & Claudia Santos, who coordinated the efforts of all those who contributed to the Quick Diagnosis, News and Views, and Book Reviews sections. Our treasurer Maury Pinsk deserves a round of applause for, among other things, finally computerizing the increasingly complicated accounting! Finally, we are certain our readers have noticed the talent of the Biomedical Communications students who produce the majority of the artwork for the Journal, including the front and back covers. Thanks to Art Directors Cynthia Yee and Beverly Nash for managing that aspect of production.

We would also like to give special thanks to all our patrons and subscribers, and especially to Diana Alli for all her support in the publication of the Abstracts from Research Day.

Overall, we have been most impressed with the talent of our peers, and we believe that our readers share this feeling. We are flattered that the students at Dalhousie's Medical School have shown interest in producing a journal similar to ours, and we wish them the best of luck in their efforts. Finally, we hope the Editors of Vol. 73 find the experience as rewarding, humbling, and most importantly, as enjoyable as we both have.

Thank you for your continued support.

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The Skin as an Immune Organ: The Role of Keratinocyte Cytokines

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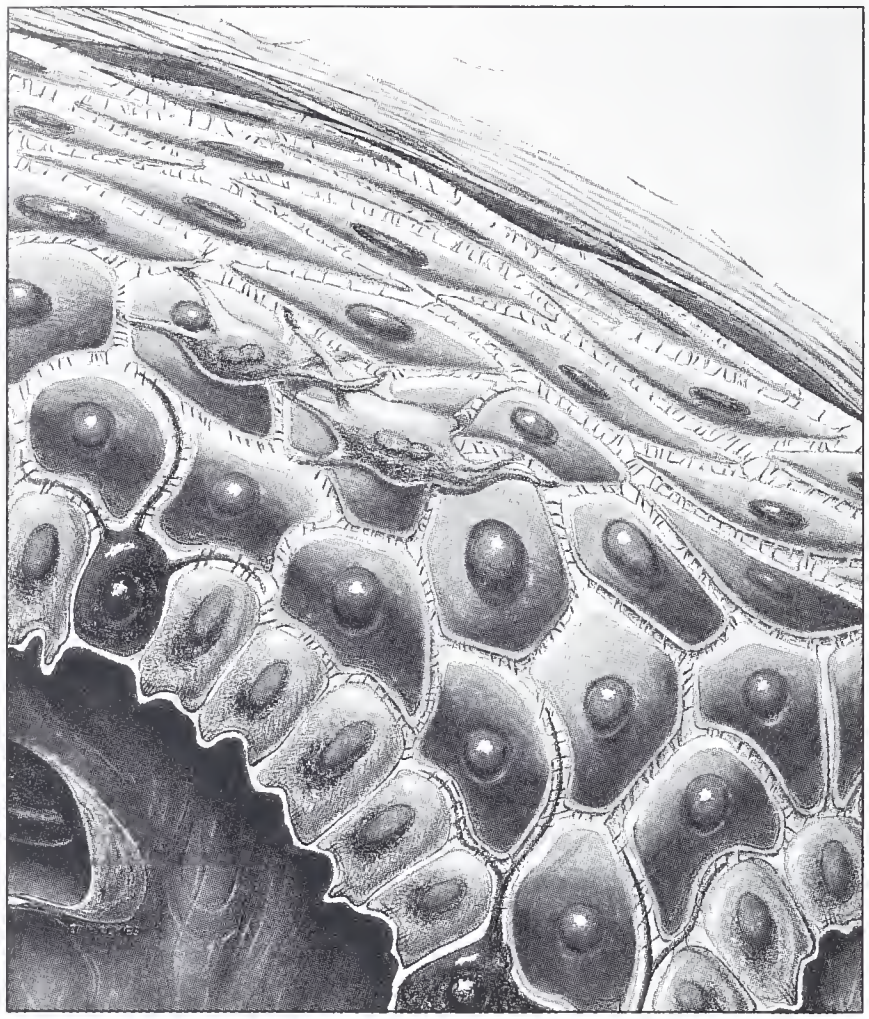
* Professor and Chief, Division of Dermatology, University of Toronto, Sunnybrook Health Sciences Centre

Abstract

The skin is the largest organ in the human body. Historically the barrier functions of the skin have been emphasized. The last ten years however, have dramatically changed our perceptions of the skin from a benign, inert, structural barrier to an active participant and initiator of immunological phenomenon. The keratinocyte has become an important participant in the immune reaction due to its immense immunoregulatory function by way of production of cytokines. Cytokine homeostasis is of importance as certain dermatological disease states have been associated with overproduction, changes in receptor status or changes in regulation of cytokines.

The following discussion reviews the literature to date in the rapidly expanding field of immunodermatology with respect to keratinocyte cytokines and their relationship to dermatological disease states. It is by understanding the fundamental pathophysiological mechanisms involved in various dermatological disease states that we can attempt to discover effective and specific treatment modalities. By blocking the action of cytokines, regulating their synthesis, release or concentration, through topical applications, we may be able to alter the underlying immune, inflammatory and proliferative responses and ultimately alleviate disease.



DUSTIN HOLMES

Introduction

The skin is the largest organ of the human body. It comprises a thickness of 0.1mm and an area of 1.5m^2 in the average 70 kg individual. The functions of the skin are diverse and include the prevention of loss of essential body fluids, the control of toxic chemical entry, ultra-violet radiation protection, regulation of body temperature and contribution to the body's supply of Vitamin D. In addition, the skin also acts a huge sensory receptor perceiving heat, cold, pain, temperature, light touch and pressure. Lastly, the skin is now recognized as the peripheral arm of the immune system.

The skin is composed of epidermis, dermis and subcutaneous tissue. The epidermis is the outer or most superficial layer of the skin and is subdivided into 4 layers: basal, prickly/spinous, granular, and horny layers. The principal cell type in the epidermis is the keratinocyte which comprises 95% of this layer's cell mass. The term "keratinocyte" is derived from the fact that these cells contribute to the tensile strength of the skin by their production of keratin[1] through a process called "keratinization". Keratinocytes are produced by mitotic division in the basal layer and ascend towards the superficial layers of the epidermis in a process that normally takes thirty days. The cells forming the horny layer or stratum corneum are fully keratinized non-viable cells. Interspersed between keratinocytes in the basal layer of the epidermis are melanocytes, the cells responsible for cellular pigment. Scattered throughout the spinous/prickly layer of the epidermis are special dendritic cells called Langerhans cells which are potent antigen presenting cells. In fact, Langerhans cells are one of the most potent antigen presenting cells in the body. While Langerhans cells are important immunocompetent cells, it is now clear that keratinocytes and melanocytes, by secreting immunoregulatory and pro-inflammatory molecules, also represent important constituents of the skin's immune system.

The dermis is a layer of connective tissue lying beneath the epidermis and makes up the bulk of the skin. The largest structural feature of the dermis are interlacing collagen fibres with some elastin. The major cellular elements of the dermis include fibroblasts, mast cells and macrophages. The dermis is also richly supplied with blood vessels and sensory receptors. The dermis is the site of the "perivascular unit" and associated endothelial cells which play an important role in the skin's immune function. Underlying the dermis is a rich layer of subcutaneous fat which separates the skin from underlying fascia and muscle.

Traditionally the skin has been thought of as an organ that plays a passive role in immunological function. That is, the skin was thought to be a target for the immune system but not an active participant and initiator of immunological phenomenon. The role of immunoregulatory cells in the epidermis of the skin has gradually been expanding[2] and it is now known that the skin has a major role in the immune response[3]. The skin's immune system has been defined as 'the cutaneous complexity of interacting immune response-related cells'[4]. The cells of importance in the skin's immune system include keratinocytes, Langerhans cells, tissue macrophages, mast cells and vascular endothelial cells[3]. These cells are of special interest for immunodermatologists due to their immense immunoregulatory function by way of production of potent molecules called **cytokines**.

Cytokines

Cytokines are heterogeneous regulatory polypeptides that function as important mediators of cell communication under normal as well as pathological conditions[5]. Cytokines posess many common characteristics in that they are 1) glycoproteins of low molecular weight, most being synthesized as larger precursor molecules, 2) very potent in the nanomolar and picomolar range, 3) able to react with specific cell surface receptors (these receptors are usually present in low numbers)[6]. Cytokines play a major role in immunoregulatory and inflammatory changes in the skin. Certain skin diseases have been associated with overproduction, changes in receptor status or changes in regulation of these powerful immune mediators[6]. Some investigators have gone so far as to state that the histopathological pattern of nearly every inflammatory skin disease can be accounted for by the appropriate cytokines or combination of cytokines[7].

In addition to the various cells traditionally thought to compose the skin's immune system outlined above, it has become increasingly apparent that the keratinocyte, the principal cell of the epidermis, can function as a significant and potent source of many of these cytokines[8]. The major classes of keratinocyte cytokines include interleukins (IL), colony stimulating factors (CSF), interferons (IFN), tumour necrosis factors (TNF) and growth factors[3]. The constitutive production of most cytokines from the keratinocyte and other immunocompetent cells in the skin is quite low[9]. However when "activated" by a variety of non-specific stimuli including chemicals, ultra-violet light, tumour promoting agents, trauma or bacterial products such as endotoxin, the keratinocyte can synthesize and secrete a vast array of powerful cytokines (Table 1).

Table 1

Cytokines Produced by Human Keratinocytes in Vitro*

Interleukins	IL-1α, IL-1ß, IL-6, IL-7, IL-8
Colony Stimulating Factors	IL-3, GM-CSF, G-CSF, M-CSF
Interferons	R IFN-α, IFN-ß
Tumour Necrosis Factors	TNF-α, TNF-ß
Transforming Growth Factors	TGF-α, TGF-ß
Growth Factors	Epidermal Growth Factor Platelet-derived Growth Factor Fibroblast Growth Factor Nerve Growth Factor

**adapted from reference 8.*

The interleukins represent a major subclass of skin cytokines. The name interleukin has been given to biologically active mediators that transmit growth and differentiation signals between various types of leukocytes. Besides keratinocytes, monocytes/macrophages, fibroblasts, Langerhans cells, mesangial cells, B-lymphocytes and natural killer cells are also interleukin producers[2]. Traditionally "interleukin-1" was the name given to the cytokine produced by the activated monocyte (an antigen presenting cell) that was essential for both T and B cell proliferation and the term "interleukin-2" was given to the lymphokine produced by activated T-cells to support T-cell proliferation[10]. Currently there are 15 identified interleukins that have a broad spectrum of biological activities including the regulation of proliferation, differentiation and migration of inflammatory and non-inflammatory cells[11].

Interleukin-1 has been one of the most widely studied and characterized of the interleukins to date. In keratinocytes, as in other cells, there are two types of IL-1 termed IL-1α and IL-1ß, two IL-1 receptors and a naturally occurring receptor antagonist. The two types of IL-1 exhibit only 30% amino acid homology yet they bind to the same receptor and have identical biological activities[5]. In most cells the IL-1ß form predominates, however in keratinocytes it is the IL-1α form that dominates. Studies have shown that IL-1 exists within the keratinocyte even in the absence of any apparent stimuli, that is, it is stored in the cells constitutively. At present it is unclear as to why there is more preformed IL-1α in the cells of the skin than IL-1ß, but its constitutive existence within the keratinocyte lends credence to the belief that the skin acts as an immune barrier against the external environment, since disruption rapidly leads to a host response[2]. Thus, damage to the

keratinocyte results in IL-1 release which in turn causes surrounding cells to release additional IL-1 that mediates various pro-inflammatory functions and amplifies the immune response[3]. In addition to its pro-inflammatory functions keratinocyte IL-1 also has autocrine functions. IL-1 also stimulates IL-6, IL-8 and GM-CSF production from neighbouring keratinocytes which are also pro-inflammatory[3], and it activates endothelial cells to express adhesion molecules for leukocytes and lymphocytes. Lymphocytes, fibroblasts, brain tissue, endothelial cells, epithelial cells, and haematopoietic stem cells can all be affected by IL-1[12]. The functions of IL-1 and other interleukins are described in Table 2.

Also of importance are the keratinocyte colony stimulating factors (haematopoietic growth factors) which include IL-3 or multi-CSF, GM-CSF, G-CSF and M-CSF. As their names suggest, they are involved in the production and action of "colonies" or haematopoietic cells. For example, multi-CSF and GM-CSF stimulate multilineage colony formation in the bone marrow whereas G-CSF and M-CSF more specifically cause granulocyte and monocyte colony formation respectively[11]. As with the other cytokines, these too are produced by various cells besides the keratinocyte and can be stimulated by immunologic reactions or infectious agent products. Colony stimulating factors interact through specific high-affinity cell membrane receptors that are expressed at various levels on haematopoietic cells[5,13]. These factors not only promote survival and proliferation of haematopoietic progenitors cells but also activate functional activities of mature blood cells[13] (Table 2).

Interferons have been described as proteins that inhibit replication of both RNA and DNA viruses by inducing new RNA and protein production. It is now known that interferons have effects on cellular proliferation and differentiation. There are three subtypes of interferons termed IFN-α, IFN-ß and IFN-γ. Lymphocytes have been shown to secrete only the γ subtype whereas several cell types can secrete the α and ß. IFN-α and IFN-ß share the same receptor, however IFN-γ's receptor is a different molecule[5]. Interferon production can be stimulated by viruses or bacteria as well as certain mitogens. As mentioned above they are involved in the control of cell growth and differentiation, the regulation of cell surface antigen expression, and modulation of both the humoral and cellular immune responses[14]. These activities are common to all types of IFN (for the most part). In the skin IFN-γ acts synergistically with TNF-α to stimulate keratinocyte production of cytokines including IL-8 as well as intercellular adhesion molecule-1(ICAM-1), enhancing immunologic and inflammatory reactions. In addition inteferons may play a part in the pathophysiology of dermatologic conditions characterized by T-cell infiltration[2].

Tumour necrosis factors were first defined as mediators responsible for haemorrhagic necrosis of tumours in animals. There have been 2 subtypes identified (Table 2); TNF-α (cachectin) and TNF-ß (lymphotoxin). TNF-α is produced by many different cells including the keratinocyte whereas TNF-ß is mainly lymphocyte derived [11]. Although

Table 2

Functions of Immunoregulatory and Proinflammatory Cytokines[2]

IL-1	Neutrophil & macrophage activation; chemotactic for T cell, B cell, natural killer cells; cytostatic & cytotoxic for certain tumour cell lines; increases collagen synthesis from fibroblasts & fibroblast proliferation; induces hepatic synthesis by certain acute phase proteins; pyrogenic and cachectic effects; increases synthesis of CSF's, IL-1, IL-2, IL-6
IL-2	T cell growth factor; induces lymphokine activated killer cells; activates cytotoxic T-cells; some effect on B cells
IL-3	Supports the growth and differentiation of pluripotent bone marrow derived stem cells; growth factor for murine mast cells
IL-4	B cell growth and differentiation factor; growth factor for T cells and mast cells
IL-5	B cell activation, growth and differentiation; eosinophil differentiationa
IL-6	Induces hepatic synthesis of acute phase plasma proteins; stimulates B cells; weak antiviral properties
IL-7	B cell and T cell proliferation
IL-8	Chemotactic for neutrophils and T lymphocytes
IL-9	T cell growth factor; mast cell growth potentiates IL-4; hematopoietic growth factors
IL-10	B cell stimulation
IL-11	Plasmacytoma proliferation; synergizes with IL-3; B cell proliferation
GM-CSF	Stimulates formation of granulocyte macrophage and, at higher concentrations, granulocyte-macrophage colonies
G-CSF	Preferentially stimulates granulocyte colonies and, at higher concentration, granulocyte-macrophage colonies
M-CSF	Stimulates macrophage colonies from pluripotent stem cells
TNF-α	Necrosis of some tumours in vivo; cytostatic for certain cell lines in vitro; many overlapping functions with IL-1
TNF-ß	Cytotoxic and cytostatic for some tumour cell lines in vitro; necrosis of some tumours in vivo, many overlapping functions with IL-1
IFN	Cytotoxic for T cells, natural killer cells, and monocytes; stimulates IL-1 and IL-2 synthesis; induces immunoglobulin production

TNF and IL-1 are structurally distinct, they share numerous properties including fever induction, and acute phase protein induction. In skin conditions there appears to be synergism between TNF and IL-1 as their biological effects seem indistinguishable[2]. In addition TNF-α has also been shown to up-regulate endothelial expression of Endothelial Leukocyte Adhesion Molecule-1 (ELAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1), as well as keratincoyte ICAM-1 (see below).

Growth factors are a family of cytokines that include epidermal growth factor (EGF), transforming growth factors (TGF), fibroblast growth factors (FGF), nerve growth factor (NGF) and platelet-derived growth factor (PDGF). These factors have been shown to have both stimulatory and inhibitory effects within the same cell and are thought to be important mediators in wound healing, fibrosis and neoplastic transformation *in vivo*[2].

Cellular Adhesion Molecules

Besides the cytokines, a group of molecules termed "cellular adhesion molecules" (CAMs) are becoming important in delineating the pathophysiology of certain dermatological disease states. Cellular adhesion molecules are cell surface proteins involved in cell-cell and cell-matrix interactions in the skin. They are becoming an increasingly popular area of investigative research due to their role in cellular trafficking. There are four main families of CAMs based on structural and sequence homology: integrins, immunoglobulin-gene, cadherins, and lectin-like glycoproteins[15]. The integrin family is further subdivided into the ß-1, ß-2 and ß-3 subfamilies. Leukocyte function antigen-1 (LFA-1) is a member of the ß-2 subfamily and is constitutively expressed on cells of lymphoid and myeloid lineage, i.e. T and B cells[16]. This antigen is important in disease states characterized by lymphoproliferation as it acts as an important mediator in T-cell migration. The immunoglobulin gene family consists of many molecules including ICAM-1 and VCAM-1. ICAM-1 is an integral membrane glycoprotein that is expressed constitutively on endothelial cells, epithelial cells and Langerhan cells. The importance of ICAM-1 is two-fold: first, it is thought to be the major ligand for LFA-1 and secondly, it can be upregulated by way of epidermal cytokines. VCAM-1 is also important for its role in cellular trafficking. ELAM-1 is a member of the lectin-like CAM family and is important in neutrophilic cellular trafficking[15].

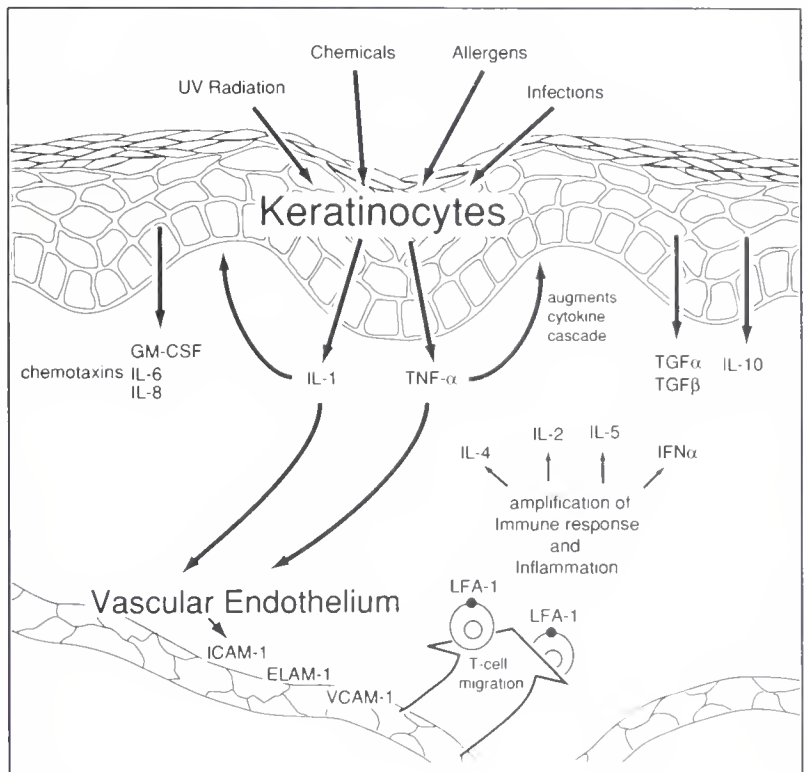


Figure 1: Simplified Scheme for Cutaneous Inflammation

IL-1, IFN-γ and TNF-α are the three principal cytokines that can influence ICAM-1 expression[15,17]. IL-1 and TNF-α can be produced by normal keratinocytes while IFN-γ is lymphocyte derived. Recently however other cytokines have been implicated in the regulation of ICAM-1 and studies have shown that IL-6, GM-CSF and M-CSF can all up-regulate the expression of ICAM-1[18]. The importance of cellular adhesion molecules in Dermatology stems from the presumption that differential expression of CAMs on the vascular endothelial cells in the dermis may contribute to differing infammatory infiltrates characteristic of certain disease states. Aberrant or exaggerated expression of adhesion molecules in epidermis or dermal microvasculature may underlie the pathophysiology of common dermatoses and many of our therapies may involve regulation of such adhesion molecules.

Pathophysiological Scheme for Cutaneous Inflammation

How do all these cytokines and CAMs interact and what is their role in skin disease? It would be beyond the scope of this article to outline all the interactions involved in the cytokine network. However by illustrating the basic fundamental mechanisms involved in diseases characterized by lymphoproliferation and T cell infiltration an appreciation can be made of the phenomenon that characterize certain common inflammatory conditions.

There are many dermatological conditions that are histologically characterized by lymphoproliferation and T-cell infiltration including benign diseases such as allergic contact dermatitis, lichen planus, psoriasis and lupus erythematosus as well as skin malignancies such as cutaneous T-cell lymphoma[5]. "How do T-cells find their way into the epidermis?" was the question that had puzzled investigators for quite some time. In the past it was always thought that the migration of T-cells into the epidermis was merely a passive event. However early in the 1980's it was discovered that keratinocytic cytokines, especially IL-1, could play an active role in activation and migration of inflammatory cells in the skin.

Presumably external stimuli including ultra-violet radiation, chemical irritants, allergens, infections and other noxious stimuli trigger an initial cutaneous inflammatory response by directly inducing keratinocytes to secrete specific pro-inflammatory cytokines and intercellular adhesion molecules[19] (Figure 1). Evidence shows that environmental stimuli causes keratinocyte production of TNF-α and/or

IL-1 within minutes to hours of skin exposure[1]. This was probably due to disruption or perturbation of keratinocytes in the superficial layers of the skin and release of preformed TNF-α and/or IL-1[20]. The release IL-1 from perturbed keratinocytes causes neighbouring keratinocytes to release more IL-1 but also IL-6, IL-8 and GM-CSF. These mediators act to augment the inflammatory responses. For instance IL-8 recruits neutrophils, macrophages and T cells to the injury where further antigen presentation can subsequently take place. IL-6 induces acute phase plasma proteins and stimulates B-cells. GM-CSF stimulates the formation of granulocyte macrophage colonies. Release of TNF from the keratinocyte allows for neighbouring keratinocytes with high affinity, empty TNF-α receptors to become "activated", with subsequent initiation of a complex cytokine cascade. TNF-α auto induction would also contribute to this cascade1. In addition, investigators have shown increases in IL-10, IFN-γ, TGF-α, TGF-ß from epidermal portions of skin exposed to superficial stratum corneum perturbations[17].

The migration of T-cells from the perivascular dermal compartment towards the epidermis requires two main factors to be operative 1) an active chemotactic gradient 2) expression of CAMs. IL-1, IL-6, IL-8 (stimulated by IL-1 and TNF-α[21]) are all cytokines produced by activated keratinocytes and possess T-cell chemotactic activity. Their secretion thus contributes to the inflammatory response via T-cell migration[22,23]. The secretion of IL-1 and TNF-α also results in activation of dermal endothelial cells and the production of the surface leukocyte adhesion molecules ICAM-1, ELAM-1, and VCAM-1. The expression of these CAMs allow for LFA-1 on the surface of T-cells to bind to their appropriate molecules, contributing to the recruitment and sequestration of predominantly memory type mononuclear cells from the circulation[7] into the dermis and epidermis[17]. It is through adhesion molecules that T cells and keratinocytes are brought into close proximity where the concentration of cytokines is high making an immune response more effective.

Once the T-cells have migrated out of the endothelium, the close apposition of mononuclear cells and keratinocytes *in vivo,* leads to amplification, both in intensity and in number, of the factors produced by these cells. The resulting proliferation of T-cells stimulates the production of more cytokines including IL-2, IL-4 and IL-5. These in turn stimulate B-cell production of antibodies[3] which exacerbates the immune response.

Other cells that may be involved in this "response to injury" type scheme include the Langerhan cell which is thought to be a source of interferon-γ. The production of γ interferon (in addition to that produced by lymphocytes) may act synergistically for keratinocyte production of ICAM-1 which is mediated by TNF-α.

Conclusions

From the discussion above it becomes apparent that there are numerous cellular and molecular interactions occurring simultaneously in the evolution of dermatological disease states. The general scheme and framework of events outlined provides a model for events that contribute to the pathophysiological processes present in many cutaneous inflammatory conditions.

By understanding the fundamental mechanisms underlying various dermatological conditions, we are one step closer in discovering specific and effective treatment modalities to halt these processes at the cellular or even molecular level and thus alleviate disease. As one well known immunder-matologist stated, by blocking the action of cytokines, regulating their synthesis and release, or increasing tissue concentrations (by topical applications) we may be able to alter the basic underlying immune, inflammatory and proliferative responses[8,24]. The last 10 years have dramatically changed our perception of the skin from an inert, structural barrier to an important, active immunological organ. Researchers are already utilizing their knowledge in the rapidly expanding and exciting field of immunodermatology in developing immunomodulatory drugs for therapeutic applications in skin diseases.

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Errata

The name of the author of the "Air Ambulance: Utilization in Southern Ontario, Patient Characteristics, and Patient Transport Routes" article in the March 1995 : Vol 72, No. 2 issue of UTMJ was incorrectly spelled in the table of contents on page 55. The name should have read Robert Paulovic.

The authors for the "Extralobar Pulmonary Sequestration and Associated Diaphragmatic Hernia" the article in the March 1995 : Vol 72, No. 2 issue of UTMJ are R. Suri B.Sc. (9T5) and R. Superina, MD.

The authors of "Shoulder Instability: Current Concepts" in the March 1995 : Vol 72, No. 2 issue of UTMJ would like to acknowledge Peter Zia (9T7) and Natalie Wong (9T8) [not Natalie Wood!!] for their assistance.

The name of one of the contributors of the Sunnybrook Emergency Room in the Quick Diagnosis Section was incorrectly spelled. The correct spelling is Jessica Macnab, MD, CCFP.

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The First Canadian Report of Hereditary Stomatocytosis in a Patient Presenting with Haemolytic Anemia Exacerbated by Yersinia Infection

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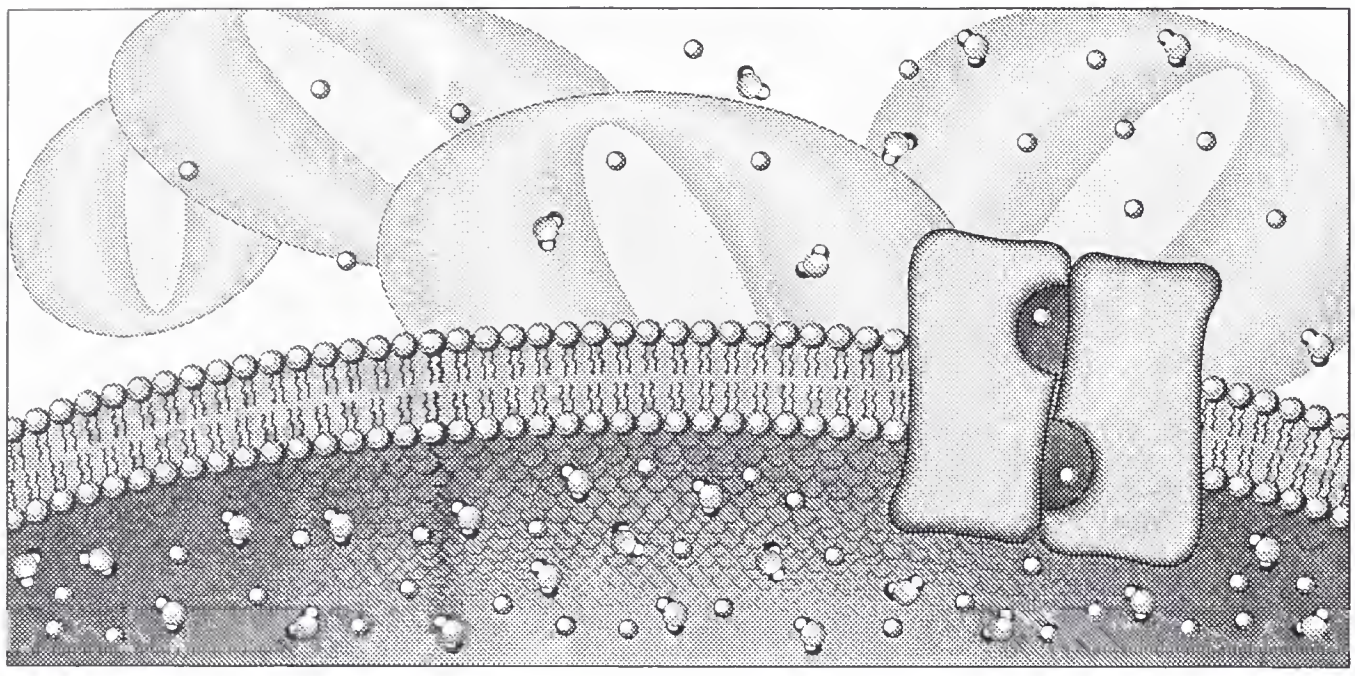

Abstract

Hereditary stomatocytosis is a rare disorder of the red blood cell membrane not previously reported in Canada. A patient known to have this disorder developed hemolytic anemia following infection with *Yersinia enterocolitica*. In this article, we review the literature on the pathophysiology of the underlying defects in hereditary stomatocytosis and its relationship with hemolytic anemia. In addition, the association between Yersinia infection and hemolysis will be discussed.

Case Report

J.W., a 27-year-old, Canadian-born man of Polish descent with a history of hereditary stomatocytosis, was transferred to The Toronto Hospital, General Division, with a recent onset of hemolytic anemia.

He was admitted to hospital with a 2 day history of fever and diarrhea. One day prior to admission, he developed right upper quadrant pain and jaundice. He had no history of nausea, vomiting, dark urine, or flu-like illness. Hematochezia, melena, chest or calf discomfort, urinary symptoms, cough, or skin rash were not present. He denied recent alcohol use. His medications included a folate supplement.

Three days later, his abdominal symptoms subsided but he complained of low back pain which required narcotic analgesia for relief. Five days after entry, his hemoglobin dropped from 110 g/L to 81 g/L without signs of external blood loss, and he was transferred to the Hematology service at The Toronto Hospital.

He was known to have had intermittent hemolytic anemia since birth. Hepatosplenomegaly was noted at 4 hours after birth and corticosteroid therapy was started at 3 months of age, and his hemoglobin seemed to stabilize. Stomatocytosis and abnormal red cell osmotic fragility was first noted at 10 months and the level of intra-erythrocytic K^+ was found to be low. At the age of 5 years, he underwent a cholecystectomy and a splenectomy, but he continued to require periodic transfusions for the hemolytic episodes which were often associated with upper respiratory tract infections. At 12 years of age, he had an episode of deep vein thrombosis with pulmonary embolism, and has been on warfarin therapy ever since. As a teenager, he abused alcohol and illicit drugs, but he had been abstinent for 6 years after an episode of alcoholic hepatitis at age 21. His last admission to hospital for a hemolytic crisis requiring blood transfusions was 7 years ago. There was no history of consanguinity and his family history was negative for hemolytic anemia.

On physical examination, his temperature was 38.3°C. He was jaundiced; no spider angiomata or petechiae were noted. Skin examination was normal. Cardiovascular and respiratory examination was unremarkable. There was no tenderness in the abdomen. The liver span was 18cm in the mid-clavicular line and the liver edge was smooth. There was no palpable abdominal mass but bowel sounds were decreased. Stool was negative for occult blood.

His initial haemoglobin following transfer was 83 g/L, leucocytes 19.8 x10^9/L (neutrophils 12.7 x10^9/L), and platelet count 905 x10^9/L. Reticulocyte count was 671 x10^9/L, with mean corpuscular volume (MCV) 113 fL (N: 76-100 fL), mean corpuscular haemoglobin concentration (MCHC) 305 g/L (N: 330-370 g/L), and red cell distribution width (RDW) 17 (N: 11-15). The blood film (Figure 1) showed stomatocytosis, polychromasia, and post-splenectomy changes including Howell-Jolly bodies and target cells. No schistocytes or spherocytes were seen.

Total bilirubin was 100 umol/L, mostly unconjugated. The aspartate aminotransferase was 41 U/L (N: 8-20 U/L), alanine aminotransferase 27 U/L (N: 8-20 U/L), and alkaline phosphatase 49 U/L (N: 20-70 U/L). Lactate dehydrogenase at initial presentation was 910 U/L (N: <200 U/L) and decreased to 259 U/L on arrival at our hospital. Haptoglobin was 0.21 g/L (N: 0.4-1.8 g/L). International normalized ratio (INR) was 1.8. Urinalysis was strongly positive for hemosiderin. Antiglobulin test was negative. Blood culture and urine culture were negative but stool culture was positive for *Yersinia enterocolitica.* Chest x-ray was normal and abdominal ultrasound showed an enlarged liver with evidence of fatty infiltration.

On the 3rd hospital day, the diarrhea and back pain resolved spontaneously, and the patient was discharged with a stable haemoglobin between 85 and 90 g/L.

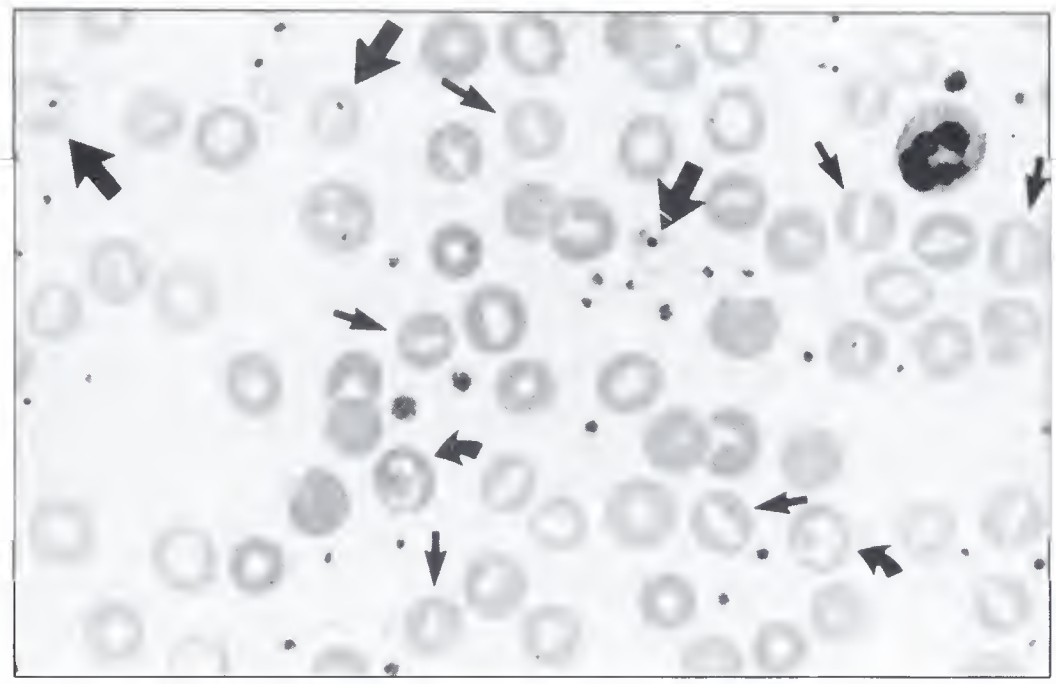

Figure 1: The peripheral blood smear of the patient: marked stomatocytosis (small arrows), polychromasia, thrombocytosis, Howell-Jolly bodies (big arrows), and occasional target cells (curved arrows). These are compatible with post-splenectomy changes and the underlying hereditary stomatocytosis disorder. *(Our thanks to Dr. Carstairs, pathologist at The Toronto Hospital, who kindly prepared the photograph.)*

Discussion

Red blood cell stomatocytosis is usually an acquired abnormality. In a study of hospitalized patients, Davidson et al[1] found that 2.3% had more than 5% stomatocytes in the routine peripheral blood films. Thirty-five percent of these had more than 20%, and 6% had greater than 50% stomatocytes. Acquired stomatocytosis is associated with acute alcoholism[2,3], and possibly with malignant neoplasms, cardiovascular or hepatobiliary disease, and some drugs (such as phenothiazine, chlorpromazine, and the combination of Ara-C and 6-thioguanine).[1,4]

Hereditary stomatocytosis was first reported by Lock et al[5] in 1961. Since then, less than 50 cases have been reported. Clinically, it is usually transmitted as an autosomal dominant trait, and is characterised by mild to moderate hemolytic anemia starting at birth although this may be delayed for up to several months. More severe forms may represent homozygosity for an autosomal recessive gene. Morphologically, the blood film may show 10% to 30% stomatocytes. The MCV is elevated, the MCHC is decreased, and the osmotic fragility is increased due to inelasticity of the red cell membrane. The anemia is not fully corrected by splenectomy although the rate of erythrocytic destruction is lessened.[6]

The pathogenesis of the hemolysis is probably multifactorial. The principle lesion is thought to be sodium leakage into the cell resulting in a rise of intracellular Na^+ and water content (hydrocytosis), and a mild decrease in intracellular K^+ [7-12]. This results in a compensatory increase in the Na^+/K^+ ATPase activity and glycolysis, but this is insufficient to correct the biochemical defect. However, in family studies of patients with hereditary stomatocytosis, Kanzaik and Yawata[13] could find no correlation between the extent of the stomatocytic changes, the severity of hemolysis, and the amount of Na^+ influx into the RBC's. Red cell membrane lipid abnormalities, such as hereditary high red cell membrane phosphatidylcholine hemolytic anemia (HPCHA)[14-17] and congenital lecithin cholesterol acyltransferase deficiency[18-20] may also be associated with stomatocytosis and impaired Na^+ transport. Abnormalities of RBC membrane proteins, particularly deficiency of band 7, may also be associated with impaired cation transport[21-23]. However, Kanzaik and Yawata[13] showed that the extent of deficiency of the integral components of band 7 was unrelated to the extent of Na^+ influx. Therefore, although there are several proposed pathophysiologic theories for stomatocytosis, the precise pathogenesis of this disorder is still not known.

In our case, the patient's hemolytic crises were generally precipitated by upper respiratory tract infections. In the present episode, severe intravascular hemolysis was asso-

ciated with *Yersinia enterocolitica* infection. The association of *Yersinia enterocolitica* infection and hemolytic anemia was reported previously in one case[24]. In that patient, the hemolysis was thought to be antibody-mediated since the direct antiglobulin test was positive. In this case, this test was negative and therefore the increased hemolysis may not have been immune-mediated.

In summary, hereditary stomatocytosis is a rare disorder of red cell membrane which is not familiar to many clinicians in North America. It is frequently associated with hemolytic anemia but the pathophysiology of this condition is controversial. Moreover, contrary to the previous report, our evidence suggested that the mechanism of hemolysis exacerbated by *Yersinia enterocolitica* gastroenteritis may not be immune-mediated and further research on this subject is required.

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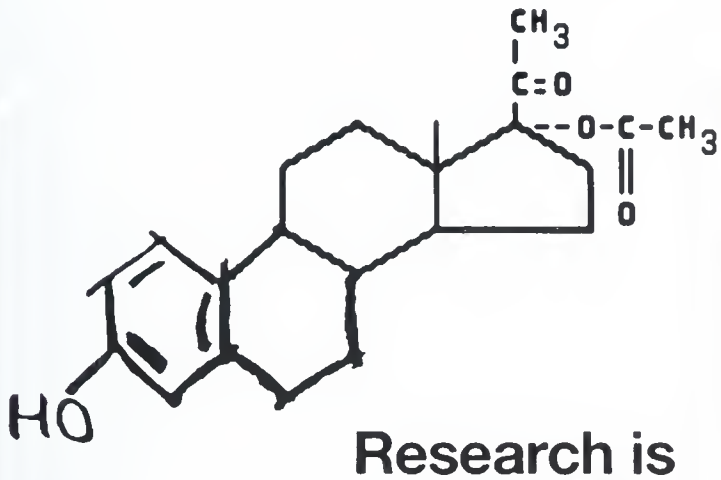

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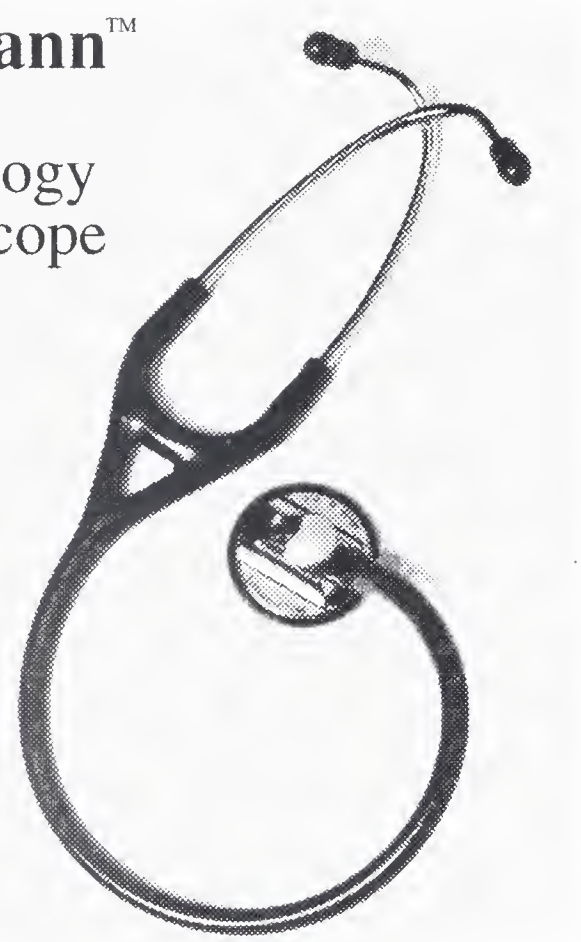

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Arterial Conduits in Coronary Artery Bypass Graft Surgery

Hari R. Mallidi (9T7) and Stephen E. Fremes, MD, MSc, FRCS(C)*

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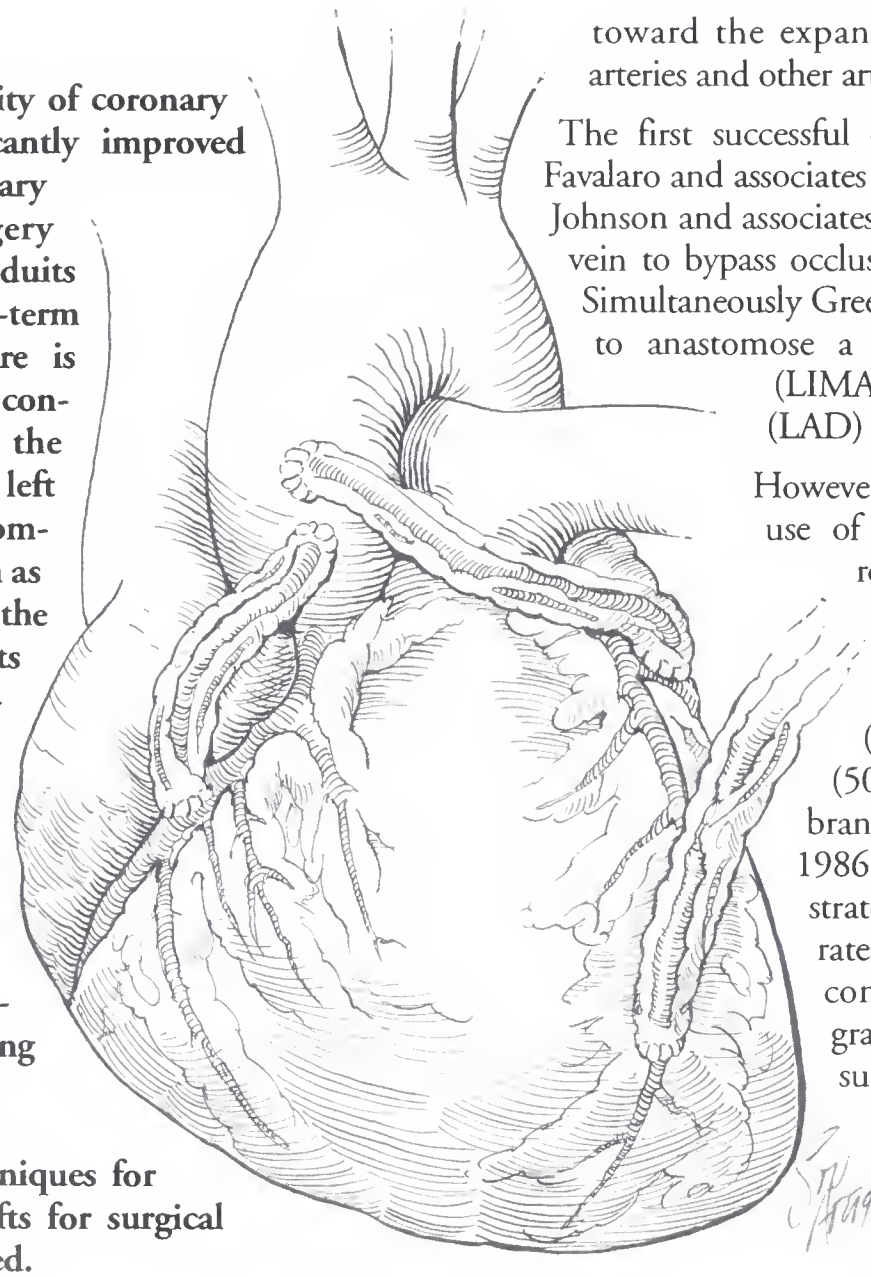
Abstract

The morbidity and mortality of coronary artery disease has significantly improved with the advent of coronary artery bypass graft surgery using saphenous vein conduits in the late 1960's. The long-term outcome of this procedure is partially dependent on the conduit used to construct the bypass. The success of the left internal mammary artery compared to the saphenous vein as a bypass conduit has led to the use of other arterial conduits including the right gastroepiploic artery, the inferior epigastric artery, and the radial artery. Cardiac surgical centres around the world have experienced favourable short-term results with these alternative arteries. However, long term results are lacking. In this paper the relevant anatomy and surgical techniques for the use of the arterial grafts for surgical revascularization is discussed.



STUART McGINNESS

Introduction

The treatment of ischemic heart disease is complex. Initially, risk factor modification and medical therapy are used. They are aimed at slowing the rate of progression of disease and the treatment of symptoms. Later in the course of the disease, revascularization by angioplasty or coronary artery bypass graft (CABG) surgery is frequently indicated either for symptomatic control or for prognostic reasons. The long-term outcome of CABG surgery is partially influenced by the conduit used. Traditionally, the saphenous vein has been the conduit of choice. However, since the early 1980's, as favourable results with the internal mammary artery graft became available, there has been a shift toward the expanded use of internal mammary arteries and other arterial conduits.

The first successful operations, were performed by Favalaro and associates at the Cleveland Clinic in 1969. Johnson and associates, also in 1969, used a saphenous vein to bypass occlusions of the left coronary artery. Simultaneously Green, used an operative microscope to anastomose a left internal mammary artery (LIMA) to the left anterior descending (LAD) artery.[1]

However, for the following ten years, the use of the LIMA for bypass surgery remained controversial. In 1984, Grondin and associates demonstrated improved 10 year patency rates with IMA (90-95%) vs. saphenous veins (50-60%) when grafted to the LAD branch of the left coronary artery.[2] In 1986, Loop and associates demonstrated favourable 10 year survival rates in patients receiving LIMA compared with saphenous vein grafts.[3] These papers established the superiority of anastomosing the LIMA to the LAD in the majority of bypass procedures. The success of this arterial conduit has lead to the expanded use of the IMA grafts, as well as the use of other arterial conduits for bypass surgery.

Rationale for the Expanded Use of Arterial Conduits

There are many reasons for using arterial conduits instead of saphenous vein conduits as bypass grafts. One of the principle problems with the use of saphenous veins as bypass conduits is the development of vein graft atherosclerosis. Studies have shown that the nature of vein graft atherosclerosis is subjectively different from that which occurs in the native coronary arteries. The onset of vein graft atherosclerosis is considerably faster than in the native circulation, and is marked by concentric intimal-fibroplasia

involving the entire length of the graft.[4] The clinical consequences of vein graft disease are recurrent angina, need for reoperation, myocardial infarction, and death.[5,6]

The results of operations with the LIMA grafts to the LAD show excellent long term patency and survival as compared with patients with saphenous vein grafts to the LAD.[2,3] One randomised study involving 80 patients showed decreased mortality and increased patency in the LIMA to the LAD group (7.7% and 94.6% respectively) compared to the saphenous vein to the LAD group (17.9% and 76.3% respectively).[7] The results of operations with bilateral mammary arteries demonstrate similar hospital morbidity and mortality but improved longterm survival, freedom from myocardial infarction, and recurrent angina when compared with patients receiving only one mammary artery.[8,9]

The improved results with single and double mammary procedures has prompted surgeons to evaluate other arterial conduits for CABG surgery, including the gastroepiploic artery, the inferior epigastric artery, and the radial artery.

Internal Mammary Artery (IMA)

Both the left and the right internal mammary arteries are used for bypass surgery. The IMA is an elastic artery with a mean proximal diameter of 2.0mm-3.0mm, and a mean distal diameter of 1.5mm-2.0mm. The average length of artery that can be harvested for use a bypass graft is 16cm. The left and right internal mammary artery (LIMA and RIMA) has been in use since the early 1970's, but the LIMA's present status as the conduit of choice for CABG was not established until after 1986.

After a median sternotomy, the internal mammary artery is exposed and dissected from the thoracic wall from above the first rib, near its origin from the subclavian artery, to the sixth intercostal space, where it divides into the superior epigastric and the musculophrenic arteries. The IMA, like all arterial conduits, is usually harvested as a pedicle with associated veins and fascia rather than as an isolated artery. The distal end of the IMA is divided, and the anterior intercostal and perforating branches are clipped. Usually, the superior end remains attached to the subclavian artery (in-situ graft). Next, the artery is dilated using dilute papaverine solution administered intraluminally and is then wrapped in a sponge soaked in papaverine solution until it is required for anastomosis to a coronary artery. This method of graft preparation is used for all the arterial conduits.

The LIMA is routed through a window in the pericardium anterior to the phrenic nerve, and is usually anastomosed to the LAD in an end-to-side manner. However, it is not uncommonly anastomosed to diagonal branches of the LAD, intermediate vessels, or obtuse marginal branches of the circumflex artery. The route of the RIMA is varied depending on the distal vessel to which it is being anastomosed. Most commonly, it is taken through a pericardial window to the right coronary artery. Otherwise, it is passed anterior to the ascending aorta when the RIMA is being grafted to the LAD or diagonal branches of the LAD. The obtuse marginals or intermediate arteries are reached by taking the RIMA through the transverse sinus.[10]

Other strategies employed to increase the utilisation of the IMA grafts include; bilateral IMA grafts, the use of free rather than in-situ grafts, and the performance of sequential grafts (more than one distal anastomosis using the same arterial graft). When the IMAs (or any other conduit) is used as a free graft it is necessary to construct two anastomoses: a distal anastomosis to the coronary artery as well as a proximal anastomosis. The later is usually constructed to the aorta, but can be constructed to a portion of a saphenous vein graft, or another IMA graft as a "Y" graft. Results with both free and sequential IMA grafts show slightly reduced patency when compared with the in-situ IMA grafts, but still superior to saphenous vein grafts.[11,12]

Results with bilateral IMA grafts have been very favorable. There is an increase in sternal wound infections in patients who receive bilateral IMA grafts. Other independent risk factors which affect the risk of sternal osteomyelitis with bilateral mammary arteries are obesity, preexisting diabetes, and old age.[13] The use of the two internal mammary arteries is not associated with increased mortality.[14,15]

Right Gastroepiploic Artery (GEA)

The right gastroepiploic artery (GEA) is a muscular artery with a mean proximal diameter of 2.5mm to 4.0mm and distal diameter of 1.25mm to 1.5mm. It has been used as a conduit for bypass surgery since the early 1980's. It has been shown to have excellent early results with 5 year patency rates of about 95%.[16,17]

The midsternal incision necessary to access the chest for CABG surgery is extended some 2 to 3 inches toward the umbilicus. This incision allows for the harvesting of RIMA, LIMA, and GEA. The next step is to ensure that a nasogastric tube is in place prior to harvesting the GEA. The right gastroepiploic artery is harvested from its origin near the pylorus as a branch of the gastroduodenal artery to the point where it forms collaterals with the left gastroepiploic artery, approximately 2/3 along the greater curve of the stomach. A length of 20cm can be harvested. The gastric branches that arise from the GEA are clipped, or ligated, as part of harvesting. After the artery has been harvested it is prepared similar to the IMA graft. Marking the axial orientation of the artery with a suture may prevent inadvertent twisting.

The GEA is generally used as an in-situ graft and less frequently as a free graft. As an in-situ graft, it is usually passed anterior to the pylorus but may be routed posterior to the stomach through the lesser sac. The pedicle then passes over the left lobe of the liver and then through a surgically created defect in the diaphragm. The optimal route, the one associated with the least amount of kinking, through the diaphragm depends on the coronary vessel to which the GEA is being anastamosed. For anastamoses to the right

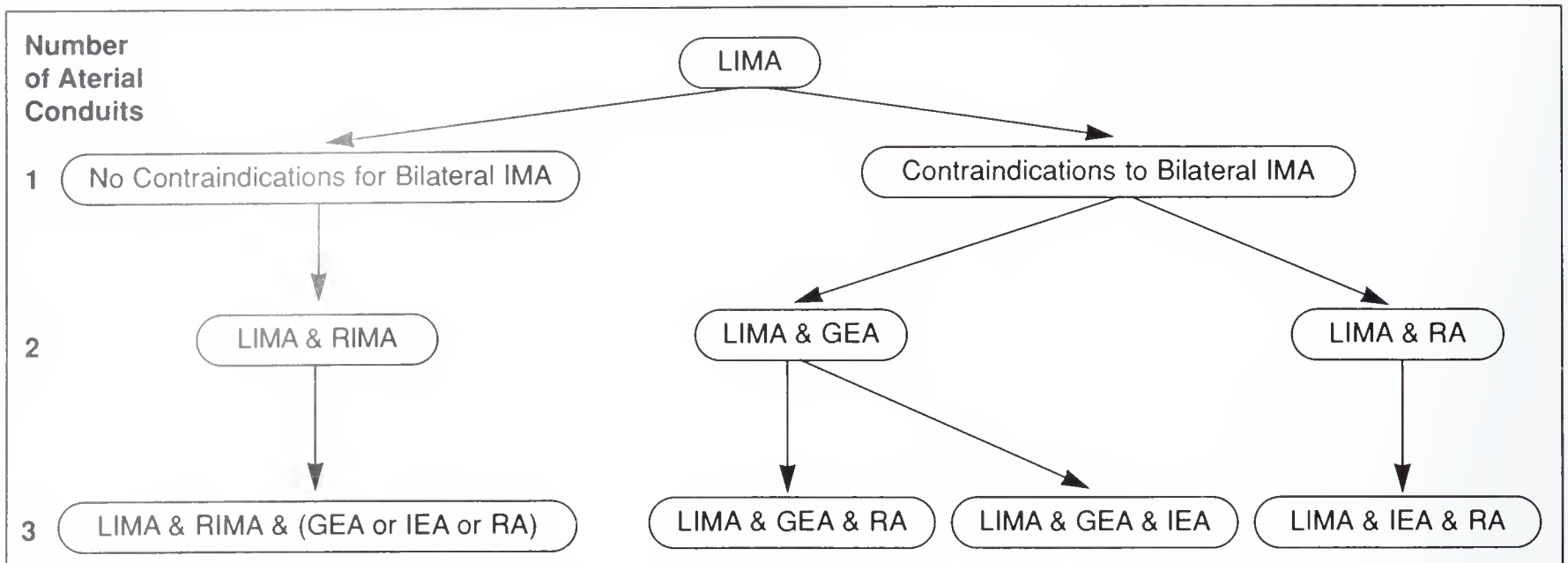


Figure 1: Flowchart for Arterial Conduit Selection
This figure demonstrates the decision making process for determining the use of arterial conduits in CABG. The contraindications for bilateral IMA grafting include diabetes mellitus, obesity, and old age. LIMA = left internal mammary artery, RIMA = right internal mammary artery, GEA = gastroepiploic artery, IEA = inferior epigastric artery, and RA = radial artery.

coronary artery system the best site for the diaphragmatic incision is paracaval. For anastamoses to the marginal branches of the circumflex artery an incision that is anteesophageal allows for least amount of kinking of the GEA.[1822]

The early results with GEA as a bypass conduit have been favourable. There are no reports of gastric ischemia or pancreatitis. However, there have been case reports of herniation through the diaphragmatic incision. As well, there have been reports of postoperative spasm, principally, of free GEA grafts.[23] Finally, there exists the possibility of injury to the graft with future gastric procedures.[24] Relative contraindications to GEA use include previous abdominal surgery, and co-existing abdominal disease.

Inferior Epigastric Artery (IEA)

The first reported use of the inferior epigastric artery was in 1988. It is a muscular artery, with a proximal diameter of 2.5mm to 3.25mm and a distal diameter of 1.5mm to 2.0mm. It is the first branch of the external iliac artery. It proceeds superiorly between the trasversalis fascia and peritoneum and pierces the rectus sheath by passing anterior to the posterior wall of the rectus sheath just superior to the arcuate line. From there it travels upward until eventually it enters the rectus muscle to anastomose with the superior epigastric artery. The total length of easily harvestable artery in one study was 11.9cm, and in another the length of the graft varied from 8cm to 13cm.[25,26]

The IEA is harvested through a left paramedian incision from the level of the umbilicus to the inguinal ligament. The rectus muscle may be retracted either medially or laterally to expose the IEA. Both the right and the left IEAs can be harvested. The branches of the IEA are ligated, or clipped, and the proximal end, near the inguinal ligament, and distal end, near the umbilicus, are ligated. After harvesting, the artery is pharmacologically dilated and prepared similar to the IMA graft.[27]

The IEA is a free graft, and its limited size allows grafting only to the first obtuse marginal, or diagonals. However, if the proximal anastamosis is to another conduit, instead of the aorta, then it is possible to graft more distal vessels of the heart.

The use of the IEA has been very limited and 5 year results are lacking. However, perioperative studies have demon-

Table 1

Patency Rates for Various Conduits Used in CABG.
LAD = left anterior descending artery, IMA = internal mammary artery, RCA = right coronary artery, GEA = gastroepiploic artery, IEA = inferior epigastric artery, and RA = radial artery.

Graft	Patency		
	Early (<1 year)	Intermediate (3-5 years)	Late (>10 years)
Saphenous Vein to LAD[33, 34]	76-92%	64-82%	55-63%
IMA[33, 34]	94%	93%	95%
in-situ IMA	—	—	76-95%
free IMA	—	—	69-92%
GEA[16, 19-21, 24, 35]	82-100%	95%	N/A
IEA[26, 28]	88-89.4%	N/A	N/A
RA[31, 36]	93.5-94.1%	N/A	N/A

strated very little increased morbidity. Postoperative complications include: abdominal wound infections[28], abdominal wound hematomas, abdominal wall necrosis including skin, subcutaneous tissue and the rectus muscle.[17] In one study, 59 of 61 IEA grafts were patent on postoperative day 10, 17 of 19 patients had patent IEA grafts at six months, and 16 of 19 had intact IEA grafts at six months.[28] Thus, it would appear that the IEA grafts are safe, however long term results are necessary before one can decide on the efficacy of these conduits.

Radial Artery (RA)

The radial artery was used in the early 1970's but was abandoned due to very high postoperative occlusion rates.[29,30] However, it has recently been reported that 3 of the RA grafts which were angiographically occluded at initial evaluation were patent at late follow-up (up to 18 years later). This suggested that graft spasm may have accounted for some of these apparent early occlusions. This prompted the use of the radial artery again, and early results were published in 1992.[31] This study included 104 patients who had 122 RA grafts. There was 1 death, 2 perioperative myocardial infarctions, and 3 cases of sternal wound infections (all in patients with bilateral IMA grafts). There were no patients with hand ischemia.

The media of the radial artery is on average 500 μm in thickness and is thicker than the IMA (330 μm), GEA (280 μm), or IEA (240 μm). This makes the radial artery anastomoses technically simpler than with the other arteries. However the radial artery does not have any vasa vasorum and it may be more susceptible to ischemia.[32] The thicker media may make the radial artery more prone to spasm.

Before harvesting the RA, the adequacy of the collateral blood flow to the hand is tested with an Allen's test and the ulnar artery is evaluated using Doppler ultrasonography. The artery is harvested with an incision from the wrist, distally, to about 2 cm distal to the cubital groove, proximally. Then, the belly of the brachioradialis is retracted, and the radial artery is dissected out. The artery is removed with its two satellite veins and surrounding fat tissue. The numerous collateral branches are clipped. After mobilisation, the artery is wrapped in a papaverine soaked sponge, and is dilated using a syringe containing a dilute solution of papaverine and verapamil. The length of artery harvested is approximately 20cm or more. The radial artery most frequently bypasses obstructions of the circumflex artery, or the right coronary artery. Since the radial artery is primarily used to complement the LIMA, it is rarely grafted to the LAD.

Potentially, the most debilitating complication that can occur when the RA is used as a graft is hand claudication. In light of this, the nondominant hand of the patient is usually selected for the source of the radial artery and patients with Raynaud's syndrome are ineligible. Another potential complication is thenar hypoaesthesia due to injury to the superficial radial nerve. Patients whose vocations require fine manual dexterity (eg. dentists, musicians, etc.) are excluded. Early results seem to indicate that the radial artery is a safe conduit for use in bypass surgery.

Conduit Selection

The selection process for choosing arterial conduits is summarized in Figure 1. Factors that determine the selection of arterial conduits include demographic information such as; age, gender, diabetes mellitus, obesity, pulmonary insufficiency, anginal class, previous abdominal surgery, left ventricular dysfunction, and coronary anatomy. The ideal candidate for multiple arterial conduits is young, of male gender, normoglycemic, with stable CCS Class II angina, good ventricular function, and triple vessel disease with proximal high-grade stenoses and good quality distal vessels. The first priority is to graft the LAD with an IMA. It is assumed patency is enhanced with in-situ arterial conduits rather than free grafts. Circumflex, and right coronary branches are bypassed preferentially with in-situ internal mammary artery, or GEA conduits where feasible. The radial artery is generally more versatile than other alternative arterial conduits and is frequently selected as the second or third arterial conduit. IEA grafts are generally selected for important diagonal branches.

Conclusion

The success of the LIMA graft to the LAD has led to the expanded use of IMA grafts, as well as the use of other arterial conduits. It is now possible to achieve total myocardial revascularization using only arterial conduits. While late results with many of the alternative arterial conduits are lacking (Table 1), it is hoped that long-term patency comparable to that achieved with IMA grafts will be demonstrated. This should result in a reduction of late ischemic events including the need for reoperation seen presently with saphenous vein conduits.

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Necrotizing Fasciitis: A Mean Strain of Strep

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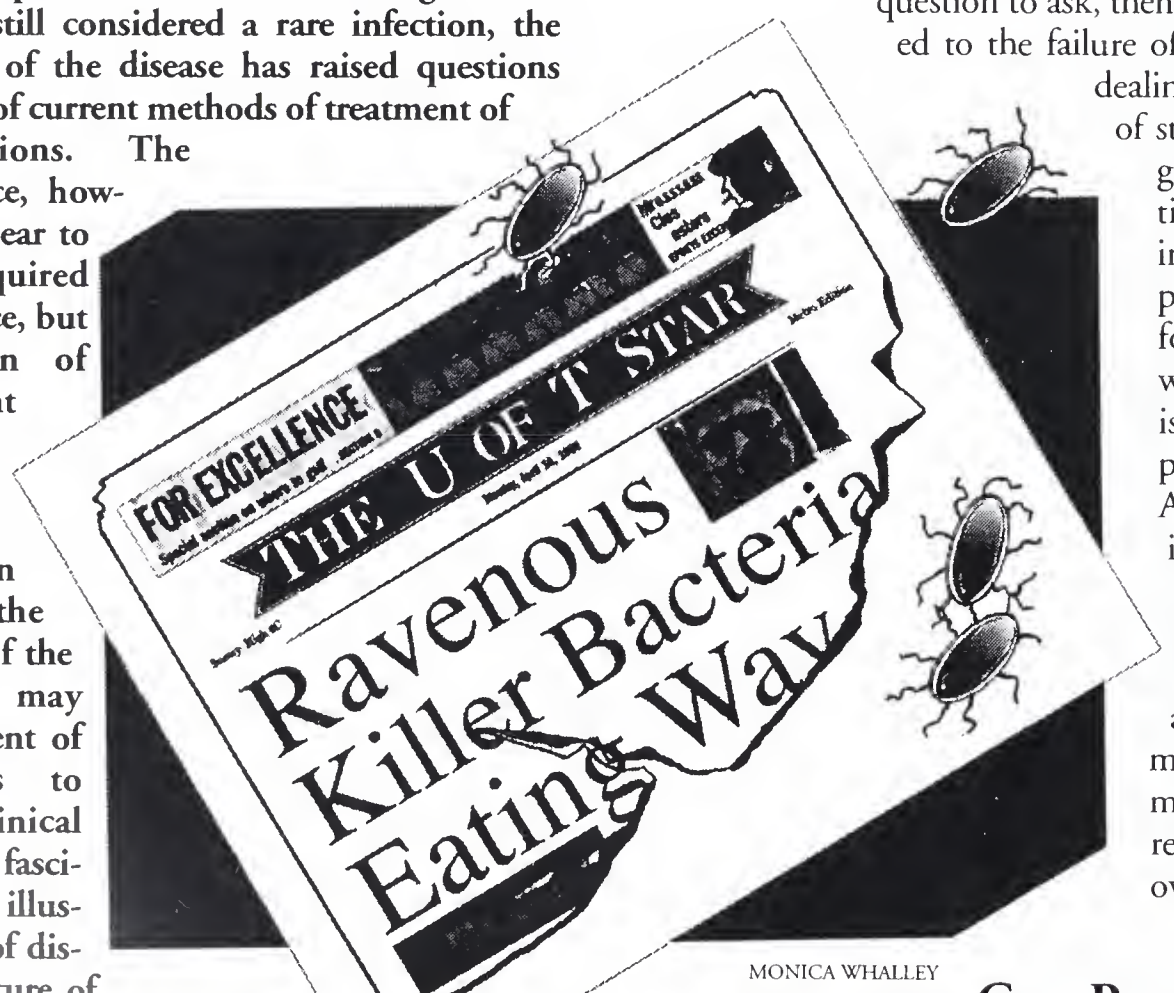
Abstract

Necrotizing fasciitis due to Group A *Streptococcus* is a soft tissue infection that has received much attention in the press lately. It is an infection that has been documented since the 1800's, and only recently received renewed interest in Ontario with an increased number of cases reported to public health units. Although necrotizing fasciitis is still considered a rare infection, the recent resurgence of the disease has raised questions about the efficacy of current methods of treatment of bacterial infections. The increased incidence, however, does not appear to be due to acquired antibiotic resistance, but rather circulation of more virulent strains of Group A *Streptococcus* in the community. Much has been learned about the pathophysiology of the infection, which may aid the development of new approaches to treatment. A clinical case of necrotizing fasciitis is presented to illustrate the rapidity of disease onset, the nature of the presenting symptoms and to guide a discussion of group A *Streptococcus* infection pathophysiology and treatment options.



MONICA WHALLEY

Introduction

With newspaper headlines such as "Ravenous killer bacteria eating way through UK"[1], it is not surprising that necrotizing fasciitis has gained so much attention in the last few years. Most notable is the form of the infection caused by *Streptococcus pyogenes*, a group A ß-haemolytic *Streptococcus*. While this disease is considered extremely rare, streptococcal infections are fairly common, causing among other diseases, strep throat (pharyngitis) and rheumatic fever[2]. Epidemiological data collected since 1990 shows an apparent increased incidence of severe soft tissue infections. Most striking is the number of reported cases in Ontario in the first three months of 1995, which has doubled over 1993-1994 figures (Dr. D.E. Low and Dr. A.E. Simor, unpublished data). The question to ask, then, is why? Is this related to the failure of antibiotics? Are we dealing with new strains of strep? Or are we just getting better at identifying the soft tissue infections? This case presentation and the following discussion will examine these issues as it pertains to patient management. A better understanding of the pathogenesis of this infection may explain why despite advances in patient management, the mortality rate has remained unchanged over the last 20 years.

Case Presentation

A 59 year old female was brought to the Emergency Department by her husband with a four day history of chills and rigors, pain, erythema and blistering in her lower left leg. She had nausea and vomiting for the last three days. There was no history of diabetes, malignancy, collagen vascular disorders, or immune-suppressing diseases or therapies. She did not use street drugs or alcohol. She had taken oral antibiotics, prescribed by her doctor, for the last three days, as well as acetaminophen with codeine for pain and fever. She did not have any chronic systemic diseases involving renal, cardiac, pulmonary or hepatic systems. She did have a history of osteoarthritis in her knees, and hypertension. The only

Figure 1: Necrotizing fasciitis at presentation.
Note erythematous bullae, blisters and dermal necrosis.

evidence of recent trauma was a closed contusion caused by hitting the affected leg against an iron bed five days previously.

On physical examination, she appeared weak and lethargic with a decreased level of consciousness. She had large purple bullae, exquisitely painful blisters and desquamation on her lower left leg (Figure 1). Her temperature was 36.7°C.; HR=88 bpm; RR=20/min; BP=140/80. Blood was drawn for chemistries. An aspirate of the bullae and blood were sent for Gram stain and culture. The patient was sent to surgery for radical debridement of the lower left leg. Pre-operative and post-operative wound swabs were also sent for culture and Gram stain. Intravenous cefotaxime and clindamycin were initiated and the patient was admitted to ICU.

Over the next 48 hours, the patient's temperature reached a maximum of 39.4°C and BP dropped to 80/60. Her blood gases indicated the development of a primary metabolic acidosis with a respiratory alkalosis. Plasma creatinine and BUN indicated that renal function was impaired as a result of decreased renal perfusion. Bilirubinemia, secondary to haemolysis, was also present. A peripheral blood smear showed toxic granulation, rouleaux formation and a marked left shift in polymorphonuclear leucocytes. Culture results showed Group A *Streptococcus* in the wound swab and blood culture (Figure 2).

She was managed with IV fluids, dialysis, cardiovascular monitoring, vasopressor agents and mechanical ventilation. Aggressive surgical treatment was carried out within 24 hours of admission with multiple debridements, open sutures and healing by second intention (Figure 3). Antimicrobial therapy, life support therapy and further surgical debridements over the following weeks resulted in the preservation of the affected limb, and resolution of the infection.

History

First observed by Hippocrates, and later characterized in the late 1800's, necrotizing fasciitis was first described as a soft tissue infection where "the skin of the affected parts melts away"[3]. In 1924, Meleney isolated *Streptococcus pyogenes*, a ß-haemolytic *Streptococcus* associated with the infection[4]. At that time, it was believed that *S. pyogenes* was the sole etiology of the soft tissue infections. However, in the last 60 years, it has been recognized that necrotizing fasciitis can involve several organisms including strict anaerobes, facultative anaerobes and strict aerobes[5,6]. However, case reports in 1994 from Gloucestershire, England once again identified an increased prevalence of *Streptococcus pyogenes* as a principle cause of necrotizing fasciitis, and so media attention has focused on a discussion that is almost 70 years old[7].

Epidemiology

Prior to 1985, most centres were reporting decreases in all streptococcal infections, most notably rheumatic fever[8]. This was likely due to the production of more effective and broader-acting antibiotics, better sanitation, better access to health care, as well as less virulent strains of *Streptococcus*[8,9]. Since 1985, however, there has been a nearly worldwide increase in the number of cases of necrotizing fasciitis[8,10], reports of a *Streptococcus*-mediated toxic shock-like syndrome, and *Streptococcus* bacteremias[8]. It is thought that the incidence of necrotizing fasciitis in Ontario, while still

Figure 2: Gram stain of blood showing Gram positive cocci in chains (*Streptococcus pyogenes*)

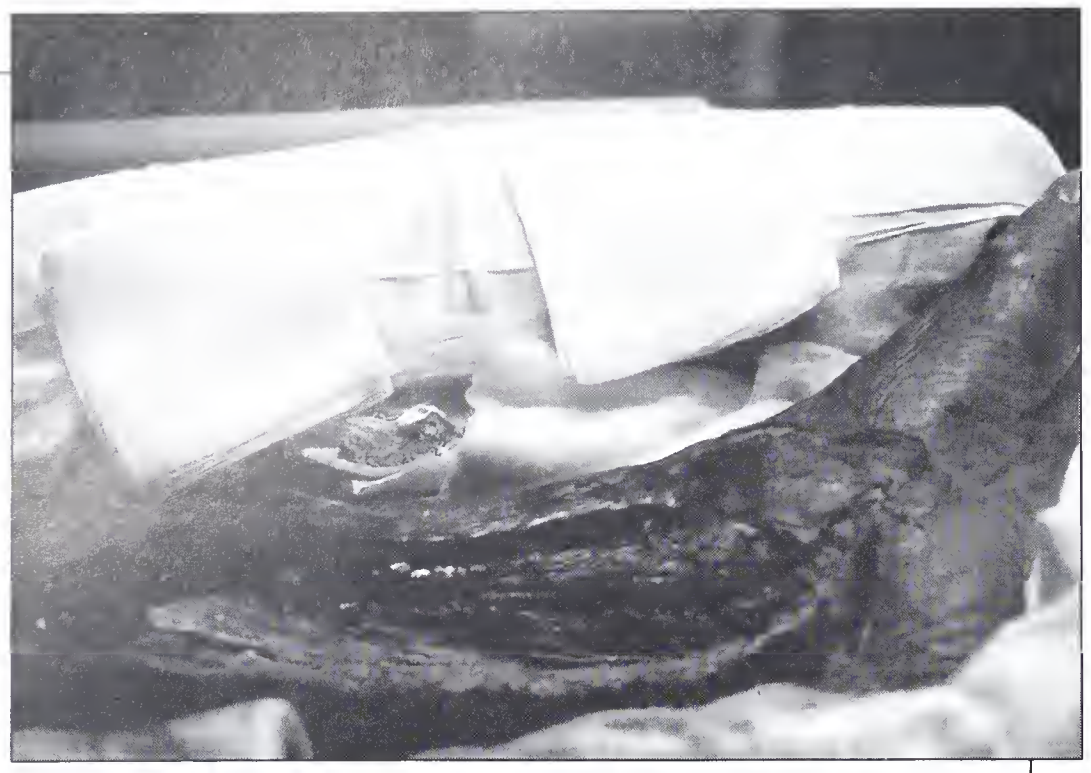


Figure 3: Necrotizing fasciitis post-debridement. All connective tissue and fat have been removed leaving muscle, bone and overlying skin intact. The patient regained use of the leg after surgical treatment.

reasonably rare (population incidence 0.18/100,000)[11], is increasing (population incidence January-March 1995: 0.3-0.4/100,000; Dr. D.E. Low and Dr. A.E. Simor, unpublished data). This data is congruous with world-wide data that suggests Group A *Streptococcus* infections have been increasing in both incidence and severity[20,12,13,14,15,16,17]. One possible explanation for this resurgence is that there is a growing prevalence of specific streptococcal serotypes to which the general population has not yet been exposed. These serotypes appear to fluctuate in prevalence over the decades, disappearing when the general population develops immunity following exposure.[8,18]

Because necrotizing fasciitis is still considered rare, it has been difficult to gather enough patient data to identify statistically significant risk factors. Several risk factors have been suggested from the literature and include diabetes[19,20,21], atherosclerosis[19], and age over 50 years[19,21]. The suggestion is that decreased tissue perfusion secondary to vascular disease predisposes to complicated infections and decreased reserve against ischemic insult[19]. In the course of necrotizing fasciitis, vascular beds may be compromised, and in those individuals with underlying disease, the end result may be more severe ischemia and necrosis[19]. Other proposed risk factors include IV drug use[5,21], a history of recent trauma or surgery (including minor contusions)[15,19], alcoholism[20], remote infection[20], pregnancy[20], immunosuppressive therapy or disease[6], collagen vascular disease[6,22], hypertension[21], malnutrition[21], obesity[21] and varicella infection[10,23]. However, many case reports have been of previously healthy individuals with no predisposing factors[10].

Pathology

Necrotizing fasciitis is one of many soft tissue infections that is specifically characterized by pale erythema of the

Table 1

Summary of Soft Tissue Infections Commonly Caused by *Streptococcus pyogenes*[1]

Infection	Population at risk	Predominant site of infection	Pain	Fever	Lesions
Impetigo	young children with poor hygiene	face and legs	not painful	no fever; patient generally looks well	red papules progressing to pustular lesions
Erysipelas	surgical patients with disrupted lymphatic drainage, CABG or DVT patients	malar area of face and lower extremities; recurrences at same site; surgical sites:	tender to touch	fever and chills, but not always present	sharply demarcated bright red area of skin with raised plateau; superficial blebs and peau d'orange can occur
Necrotizing fasciitis	no confirmed risk groups	extremities or trunk	severe pain, progressing to anaesthesia later in infection	malaise, fever and chills; patient may appear toxaemic	minimal erythema early in the infection, progressing to dusky, mottled erythema, edema, and large purple bullae

Legend: Infections are listed in order of increasing severity and poorer prognosis.
Abbreviations: DVT: deep vein thrombosis; CABG: coronary artery bypass graft procedure.

affected skin without distinctive borders[19]. Blisters or bullae are usually present containing red and black fluid, and the erythema quickly progresses to purplish discoloration[19]. The pathological basis for the change in colouration is due to progressive thrombosis of the microvasculature as invasion proceeds, leading to ischemic changes in the skin[24,25]. Mild or moderate edema is usually present[19,24]. Pathologically, only the fascia and subcutaneous fat are involved in the infection. Later, with ischemic changes and necrosis, the overlying skin is involved with a sharply demarcated area of necrosis surrounded by erythema[24] and anaesthesia due to ischemic damage to local nerve endings[19]. Usually necrotizing fasciitis does not involve deeper tissues, but if infection spreads into the muscular fascial envelope, myonecrosis can occur[5,19]. The infection may also produce toxic effects in some patients including lethargy, disorientation, and end organ disease[19]. These characteristics distinguish necrotizing fasciitis from other soft tissue infections (Table I, for more detailed discussion, the reader is referred elsewhere[6,10,19,25]). The infection is also characterized by a high mortality rate, which is proportional to the extent of infection at the time of presentation and the time taken to initiate therapy[4,5,19]. The reported mortality figures are between 30%-50% with aggressive treatment[5,10,20,22,26].

Pathogenesis

Many people will become infected with group A haemolytic *Streptococcus*, which will likely manifest as strep throat, erysipelas, or cellulitis. The vast majority of these people will not go on to develop necrotizing fasciitis caused by group A *Streptococcus*. The explanation for this phenomenon lies in the discovery of specific pathogenic mechanisms in some strain groups of Group A *Streptococcus* that leads to invasive, necrotizing infections. Absence of these mechanisms leads to infections that can be easily resolved with conservative antibiotic treatment. The first of these mechanisms involve M proteins. *S. pyogenes* strains vary in the serotype of M proteins, proteins that are bacterial cell wall components and have been shown to inhibit phagocytosis by binding of fibrinogen and blocking complement mediated opsonization[27]. In fact, a substantial proportion of invasive strains present today have been shown to be M-1 or M-3 type specific[10,28], although M antigens may vary widely in different geographic areas[28]. One theory to explain the resurgence of *Streptococcus pyogenes* infections is that these serotypes cycle through the years, becoming more prevalent at one time, and receding with the onset of population immunity[18]. A second pathologic mechanism involves a series of pyrogenic secretory products: exotoxins A, B and C, mitogenic factor and streptococcal superantigen. These secreted products play a role in the disease process by promoting production of human cytokines[18], but also mediate a toxic shock response through their activities as superantigens[28,29]. Superantigens are proteins that interact with T cell receptors and MHC molecules to promote activation of up to 25% of the body's T cells in a non-specific manner with proportionately high cytokine production[28,29]. Along with cytokine production inducing shock, cytokines also induce apoptosis in T cell subpopulations, leading to depletion of these T cell subgroups. Superantigen secretion is also important in the context that bacteria may acquire increased pathogenicity via a transducing bacteriophage carrying a superantigen gene[30]. Aside from the superantigen activities of some secreted proteins, there is also some evidence that a cysteine protease is associated with the invasiveness of the *Streptococcus* organism into fascia[31]. It is believed that cysteine protease acts to cleave IL-1ß into an active product that mediates shock and inflammation[32], in addition to degrading extracellular matrix proteins such as fibronectin and vitronectin, leading to increased invasiveness and progression of infection[32]. The presence, and indeed larger quantities of each of these bacterial cell products are what differentiate invasive group A streptococcal infections causing necrosis and group A streptococcal infections that progress only to a sore throat with flu-like symptoms[2].

Treatment

Necrotizing fasciitis is an infection requiring surgical intervention as well as antibiotic therapy. It is essential that blood cultures and swabs of infected tissues be cultured for aerobic and anaerobic organisms[33]. Gram staining is also useful as it provides a crude identification of organisms that can help guide antibiotic therapy in the short term[2,33]. Initial treatment in the Emergency Room included cefotaxime, a third generation cephalosporin with a high degree of ß-lactamase resistance. Cefotaxime offers good coverage of Gram positive and Gram negative aerobes (eg: *Streptococcus sp.*), but poor bactericidal effects on anaerobes[34]. It is however, less effective against *Staphylococcus*, a common coinfectant with Streptococcal infections[34]. Penicillin has also been shown to be effective against streptococcal infections[9,35], especially when used in combination with clindamycin[7,18]. Clindamycin also has specific anti-streptococcal activity, can act synergistically with other antibiotics and is believed to reduce toxaemia in necrotizing fasciitis by binding to and sequestering streptococcal exotoxins[34,36]. A more experimental treatment exists for treating refractory shock and toxaemia that involves the intravenous administration of polyclonal anti-streptococcal immunoglobulin[37]. The immunoglobulin acts to neutralize exotoxins produced by the bacteria, leading to improvement of the patient's condition[37].

Immediately after the patient has been stabilized, wound exploration is performed with culture of the intraoperative wound. Necrotic tissue and infectious material is removed by radical debridement, and usually the wound is left open and packed with sterile saline-soaked dressings. Frozen section examination of the debrided tissue can also be useful in assisting in the identification of the infecting organism. Wound exploration is again performed within 24 hours with further debridement. The purpose of repeated surgery is to open access of the infected site to the IV antibiotics and to decrease the microbial load on the patient[2]. Occasionally

antibiotics may be dripped into the site of infection to facilitate drug delivery[22,25].

As the wound begins to heal, the split tissue is slowly apposed to decrease the size of the debridement site. This allows smaller skin grafts to be used, as surgery now turns to wound closure.

Conclusion

Necrotizing fasciitis is a severe, quickly progressing soft tissue infection that appears to be increasing in several industrialized centres. The infection pathophysiology is related to systemic response of the host to toxic bacterial cell products, leading inevitably to necrosis, end organ failure and death. The use of appropriate antibiotics, the treatment of infection complications and early surgical intervention are hallmarks of patient management that attempt to reduce the mortality of necrotizing fasciitis due to Group A *Streptococcus*. However, it is the ability to diagnose this disease early which gives the patient the best chance at survival.

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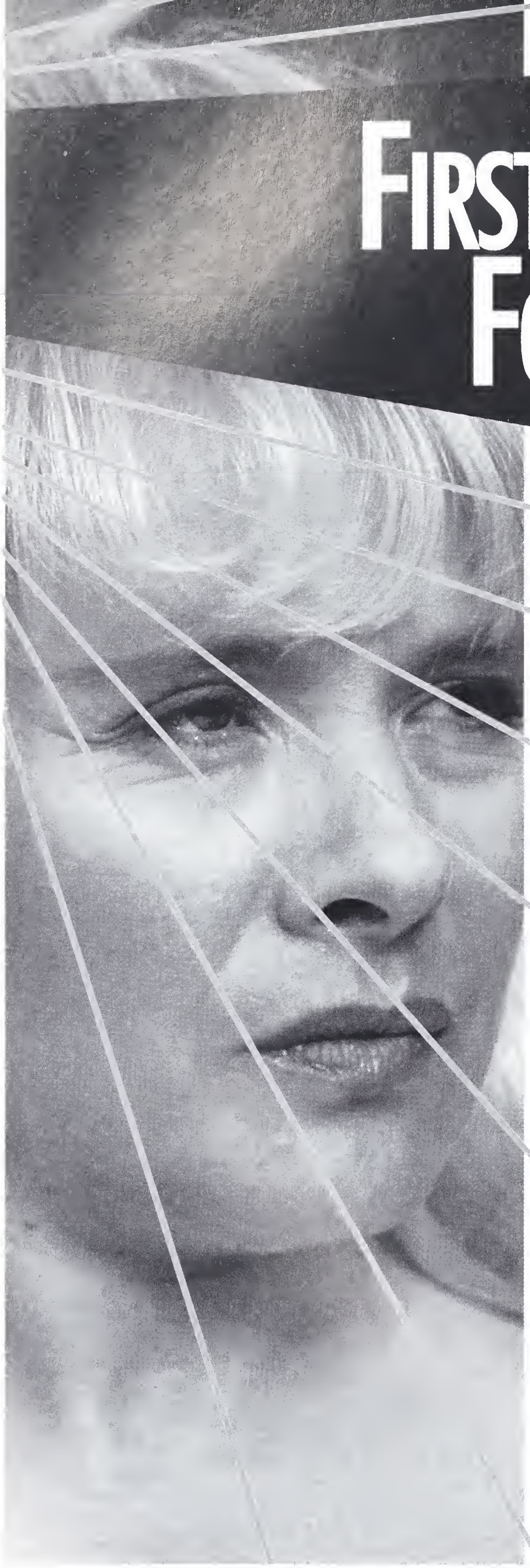

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INDICATIONS — PROZAC (fluoxetine) may be indicated for the symptomatic relief of depressive illness.

CONTRAINOICATIONS — PROZAC (fluoxetine) is contraindicated in patients with known hypersensitivity to the drug. *Monoamine Oxidase Inhibitors* – There have been reports of serious, sometimes fatal, reactions in patients receiving PROZAC in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued PROZAC and then started on an MAOI. PROZAC should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping PROZAC before starting an MAOI.

WARNINGS — Allergic Reactions (Rash and Accompanying Events): Of 5,600 patients given fluoxetine approximately 4% developed a rash and/or urticaria. Almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Reported in association with these allergic reactions include rash, fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely. Two patients are known to have developed a serious cutaneous systemic illness. One was considered to have a leukocytoclastic vasculitis, and the other severe desquamation that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic manifestations suggestive of serum sickness. Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Oeath has been reported to occur in association with these systemic events. Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported. Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely These events have occurred with dyspnea as the only preceding symptom. Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, PROZAC should be discontinued

Implications of the Long Elimination Half-Life of Fluoxetine: Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment.

PRECAUTIONS — Nervousness and insomnia were reported by 10 to 15% of patients treated with PROZAC (fluoxetine). These symptoms led to discontinuation of the drug in 5% of the patients. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with PROZAC. Hypomania or mania occurred in approximately 1% of fluoxetine treated patients. The incidence of seizures associated with fluoxetine during clinical trials did not appear to differ from that reported with other marketed antidepressants; however, patients with a history of convulsive disorders were excluded from these trials. The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. High risk patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization. Prescriptions for fluoxetine should be written for the smallest quantity of drug consistent with good patient management. PROZAC should be used cautiously in patients, especially those with diseases or conditions that could affect metabolism or hemodynamic responses. PROZAC has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Retrospective evaluation of EKGs in these studies showed no conduction abnormalities that resulted in heart block. The mean heart rate was reduced by approximately 3 beats/minute. In patients with diabetes, fluoxetine may alter glycemic control. Hypoglycemia has occurred during therapy with fluoxetine, and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with fluoxetine is instituted or discontinued. Patients should be cautioned against driving an automobile or performing hazardous tasks until they are reasonably certain that treatment with PROZAC does not affect them adversely. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients. Cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when PROZAC was discontinued. Some cases were possibly due to SIAOH. The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role. **Use in Pregnancy and Lactation:** Safe use of fluoxetine during pregnancy and lactation has not been established. Therefore it should not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the child or fetus. **Use in Children:** Safety and effectiveness in patients below the age of 18 have not been established. **Use in the Elderly:** Elderly patients should initially receive fluoxetine in low dosage with slow progressive increases only if required and tolerated. Patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly should be under careful observation at all dosage levels.

DRUG INTERACTIONS — There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when PROZAC has been administered in combination with these agents. Five patients receiving PROZAC in combination with tryptophan experienced adverse reactions, including agitation, restlessness and gastrointestinal distress. There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly. Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs.

AOVERSE REACTIONS — The most commonly observed adverse events associated with the use of PROZAC (fluoxetine) and not seen at an equivalent incidence among placebo treated patients were: central nervous system complaints, including headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, and dizziness or lightheadedness; gastrointestinal complaints, including nausea, diarrhea, dry mouth and anorexia, and excessive sweating Fifteen percent of approximately 4,000 patients who received PROZAC in North American clinical trials discontinued treatment due to an adverse event The more common events causing discontinuation included psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (2.4%), primarily dizziness, asthenia, and headaches; skin (1.4%), primarily rash and pruritus. Suicidal thoughts and acts are far more common among depressed patients than in the general population. It is estimated that suicide is 22 to 36 times more prevalent in depressed persons than in the general population. A comprehensive meta-analysis of pooled data from 17 double-blind clinical trials in patients with major depressive disorder compared fluoxetine (n=1765) with a tricyclic antidepressant (n=731) or placebo (n=569), or both. The pooled incidence of emergence of substantial suicidal ideation was 1 2% for fluoxetine, 2.6% for placebo, and 3.6% for tricyclic antidepressants The following adverse reactions, arranged by body system, were reported on at least one occasion by patients during treatment with PROZAC either during clinical trials or after marketing. **Allergic or Toxic:** rash, pruritus. Infrequent: chills and fever, urticaria, maculopapular rash. Rare: allergic reaction, erythema multiforme, vesiculobullous rash, serum sickness, contact dermatitis, erythema nodosum, purpuric rash, leukocytoclastic vasculitis, leukopenia, thrombocytopenia, arthralgia, angioedema, bronchospasm, lung fibrosis, allergic alveolitis, larynx edema, respiratory distress. **Neurologic:** headache, tremor, dizziness or lightheadedness, asthenia Infrequent: abnormal gait, ataxia, akathisia, buccoglossal syndrome, hyperkinesia, hypertonia, incoordination, neck rigidity, extrapyramidal syndrome, convulsions, photophobia, myoclonus, vertigo, migraine, tinnitus, hypesthesia, neuralgia, neuropathy, acute brain syndrome. Rare: dysarthria, dystonia, torticollis, decreased reflexes, nystagmus, paralysis, paresthesia, carpal tunnel syndrome, stupor, coma, abnormal electroencephalogram, chronic brain syndrome, dyskinesia and other movement disorders (including worsening of preexisting conditions or appearance in patients with risk factors [eg, Parkinson's disease, treatment with neuroleptics or other drugs known to be associated with movement disorders]), neuroleptic malignant syndrome-like events. **Behavioural:** insomnia, anxiety, nervousness, agitation, abnormal dreams, drowsiness and fatigue Infrequent: confusion, delusions, hallucinations, manic reaction, paranoid reaction, psychosis, depersonalization, apathy, emotional lability, euphoria, hostility, amnesia, increased libido. Rare: antisocial reaction, hysteria, suicidal ideation, violent behaviours **Autonomic:** excessive sweating Infrequent: dry mouth, constipation, urinary retention, vision disturbance, diplopia, mydriasis, hot flushes. **Cardiovascular:** Infrequent: chest pain, hypertension, syncope, hypotension (including postural hypotension), angina pectoris, arrhythmia, tachycardia. Rare: bradycardia, ventricular arrhythmia, first degree AV block, bundle branch block, myocardial infarct, cerebral ischemia, cerebral vascular accident, thrombophlebitis. **Gastrointestinal:** nausea, disturbances of appetite, diarrhea. Infrequent: vomiting, stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, melena, thirst, abnormal liver function tests. Rare: bloody diarrhea, hematemesis, g.i. hemorrhage, duodenal ulcer, stomach ulcer, mouth ulceration, hyperchlorhydria, colitis, enteritis, cholecystitis, cholelthiasis, hepatitis, hepatomegaly, liver tenderness, jaundice, increased salivation, salivary gland enlargement, tongue discolouration, fecal incontinence, pancreatitis. **Respiratory:** bronchitis, rhinitis, yawn. Infrequent: asthma, dyspnea, hyperventilation, pneumonia, hiccups, epistaxis. Rare: apnea, lung edema, hypoxia, pleural effusion, hemoptysis. **Endocrine:** weight loss. Infrequent: generalized edema, peripheral edema, face edema, tongue edema, hypoglycemia, hypothyroidism, weight gain. Rare: dehydration, gout, goitre, hyperthyroidism, hypercholesteremia, hyperglycemia, hyperlipemia, hyperprolactinemia, hypokalemia, hyponatremia, iron deficiency anemia, syndrome of inappropriate AOH secretion. **Hematologic:** Infrequent: anemia, lymphadenopathy, hemorrhage. Rare: bleeding time increased, leukocytosis, lymphocytosis, thrombocytopenia, thrombocytopenic purpura, thrombocythemia, retinal hemorrhage, petechia, purpura, sedimentation rate increased, aplastic anemia, pancytopenia, immune-related hemolytic anemia. **Oermatologic:** Infrequent: acne, alopecia, dry skin, herpes simplex. Rare: excema, psoriasis, seborrhea, skin hypertrophy, skin discolouration, herpes zoster, fungal dermatitis, hirsutism, ecchymoses. **Musculoskeletal:** muscle pain, back pain, joint pain. Infrequent: arthritis, bone pain, bursitis, tenosynovitis, twitching. Rare: bone necrosis, osteoporosis, pathological fracture, chrondrodystrophy, myositis, rheumatoid arthritis, muscle hemorrhage. **Urogenital:** painful menstruation, sexual dysfunction, urinary tract infection, frequent micturition. Infrequent: abnormal ejaculation, impotence, menopause, amenorrhea, menorrhagia, ovarian disorder, vaginitis, leukorrhea, fibrocystic breast, breast pain, cystitis, dysuria, urinary urgency, urinary incontinence. Rare: breast enlargement, galactorrhea, abortion, dyspareunia, uterine spasm, vaginal hemorrhage, metrorrhagia, hematuria, albuminuria, polyuria, pyuria, epididymitis, orchitis, pyelonephritis, salpingitis, urethritis, kidney calculus, urethral pain, urolithiasis. **Miscellaneous:** chills. Infrequent: amblyopia, conjunctivitis, cyst, ear pain, eye pain, jaw pain, neck pain, pelvic pain, hangover effect, malaise. Rare: abdomen enlarged, blepharitis, cataract, corneal lesion, glaucoma, iritis, ptosis, strabismus, deafness, taste loss, moniliasis, hydrocephalus, LE syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSAGE — There were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline. One other patient who reportedly took up to 3000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific treatment. Since vomiting occurred, the amount of drug absorbed may have been less than that ingested. Since introduction, reports of death attributed to overdosage of fluoxetine alone have been rare. **Symptoms:** Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation, including seizures.

DOSAGE AND AOMINISTRATION — Since it may take up to four or five weeks to reach steady-state plasma levels of PROZAC (fluoxetine), sufficient time should be allowed to elapse before dosage is gradually increased. Higher dosages are usually associated with an increased incidence of adverse reactions. **Initial Adult Dosage:** The recommended initial dosage is 20 mg administered once daily in the morning A gradual dose increase should be considered only after a trial period of several weeks if the expected clinical improvement does not occur. Dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited. During maintenance therapy, the dosage should be kept at the lowest effective level. A lower or less frequent dosage should be used in patients with renal and/or hepatic impairment and in those on multiple medications **Use in the Elderly:** A lower or less frequent dosage is also recommended in the elderly **Use in Pediatrics:** The safety and effectiveness of PROZAC in the pediatric age group has not been established

AVAILABILITY — PROZAC (fluoxetine hydrochloride) 10 mg capsules are green and grey, printed with Lilly 3104 and Prozac 10 mg, packaged in amber HDPE bottles of 100 DIN 02018985

PROZAC (fluoxetine hydrochloride) 20 mg capsules are green and white, printed with Lilly 3105 and Prozac 20 mg, packaged in amber HDPE bottles of 100. DIN 00636622

PROZAC (fluoxetine hydrochloride) liquid is a clear colourless syrup solution 20 mg/5 mL, an odour of mint, packaged in amber glass bottles of 120 mL (M-5120). DIN 01917021

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Bringing Research to Life

The Anterior Cruciate Ligament: Diagnosis and Treatment Options

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Abstract

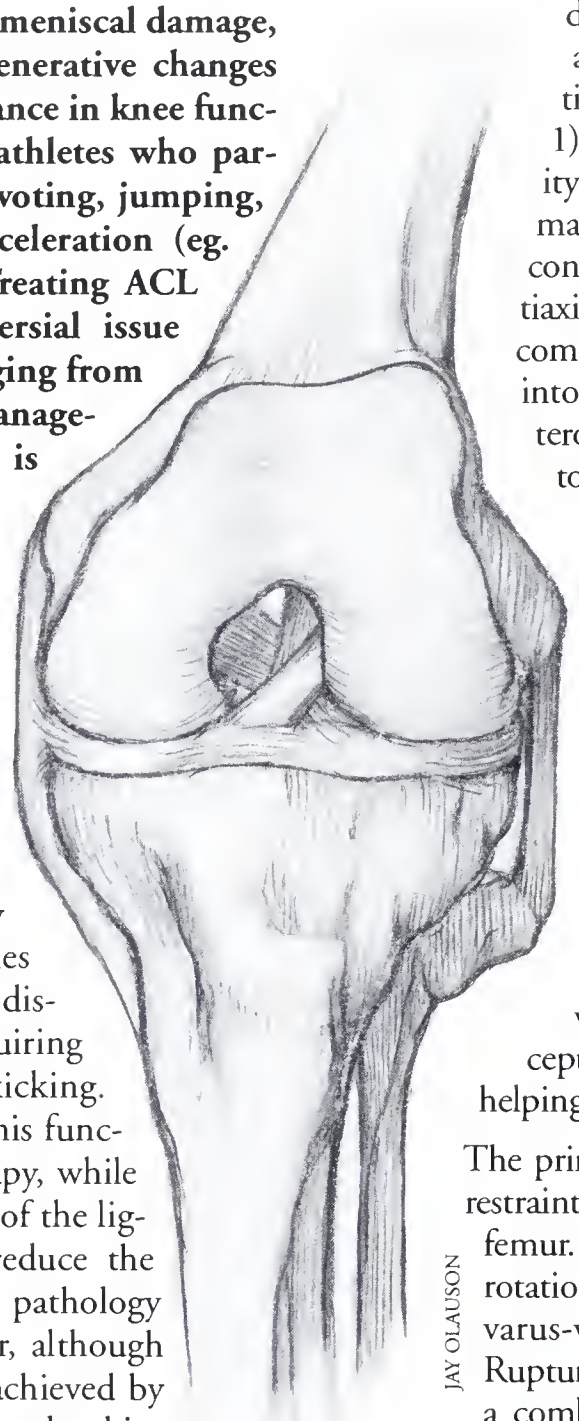
Injury to the anterior cruciate ligament (ACL) is one of the most common and debilitating injuries to the knee. ACL insufficiency often results in decreased stability, function, increased risk of meniscal damage, and possible increased risk of degenerative changes within the joint. The ACL's importance in knee function is especially evident in those athletes who participate in activities that require pivoting, jumping, cutting, and rapid acceleration-deceleration (eg. football, basketball, soccer etc.). Treating ACL injuries has long been a controversial issue with various treatment options ranging from conservative (ie. non-operative) management to reconstructive surgery. It is hoped that this review article will provide the reader with an understanding of the current thinking and controversies surrounding this ligamentous injury.

Introduction

The anterior cruciate ligament (ACL) has been one of the most extensively studied ligaments in the body. Injuries to the ACL often result in functional disability particularly in activities requiring pivoting, jumping, cutting, and kicking. Some patients can accommodate to this functional loss through conservative therapy, while others require surgical reconstruction of the ligament to provide stability and to reduce the incidence of subsequent injuries and pathology associated with instability[1,2]. However, although an improvement in function can be achieved by present operative techniques, the complex biologic, physiologic, and mechanical characteristics of the normal ACL cannot be fully restored. This article will present and discuss the current diagnostic, investigational, and treatment options as well as the controversies associated with them.

Anatomy and Function

The ACL is an intracapsular but extrasynovial cordlike structure coursing through the middle of the knee within the intercondylar notch. It originates from the posteromedial portion of the lateral femoral condyle and inserts into the anterior aspect of the tibial plateau next to the tibial spines (Figure 1). The ligament has a degree of viscoelasticity that allows it to stretch and return to normal length without damage. It has a physical configuration with multiple fibers and a multiaxial function that guide the knee through its complex motions. The ACL can be divided into an anteromedial component and a posterolateral component allowing the ligament to be functional in all degrees of flexion and extension. The anteromedial portion is taut during flexion while the posterolateral portion is tighter in extension.



JAY OLAUSON

The ligament's predominant blood supply, the middle genicular artery, arises from the popliteal artery and pierces the posterior capsule. Vascularization also occurs via the infrapatellar fat pad from the inferior medial and lateral genicular arteries[2,3].

The ACL also contains nerve fibers which transmit pain as well as mechanoreceptors that provide proprioceptive senses, helping to protect the knee during use.

The primary function of the ACL is to serve as a restraint to limit anterior tibial displacement on the femur. It also acts as a secondary restraint to tibial rotation (especially during full extension), and to varus-valgus angulation at full extension. Rupture or chronic deficiency of the ACL allows a combination of abnormal anterior translation and rotation of the tibia[3].

Many concomitant injuries to other ligaments, menisci, chondral, subchondral osseous, and posterior soft tissues can occur in the acute disruption of the ACL[4]. These associated injuries will determine whether a knee will have a good prognosis or not[5,6,7,8].

Diagnosis and Investigations

Clinical

The diagnosis of an ACL injury can most often be made clinically. The injury usually occurs with a history of the patient participating in a high demand activity while changing direction suddenly or landing from a jump. A "pop" may have been heard or felt at the time of injury accompanied by acute pain, instability, and difficulty weight bearing with inability to continue his/her activities. Hemarthrosis causing swelling is noted within a few hours and is a good indicator of ACL damage if a fracture has been ruled out. The ACL is partially or completely torn in 70-80% of those patients who sustain an acute traumatic hemarthrosis to the knee[9,11,12,13].

It is important to remember that the patient must be relaxed and be comfortable before a careful physical examination is carried out. The results of the physical examination of the injured knee must be compared with those of the normal knee. If a tense effusion is present with severe pain, aspiration may provide relief and it also allows examination of the aspirate for the presence of blood.

Physical maneuvers to demonstrate ACL insufficiency include the Lachman, anterior drawer, and pivot shift tests[9,10].

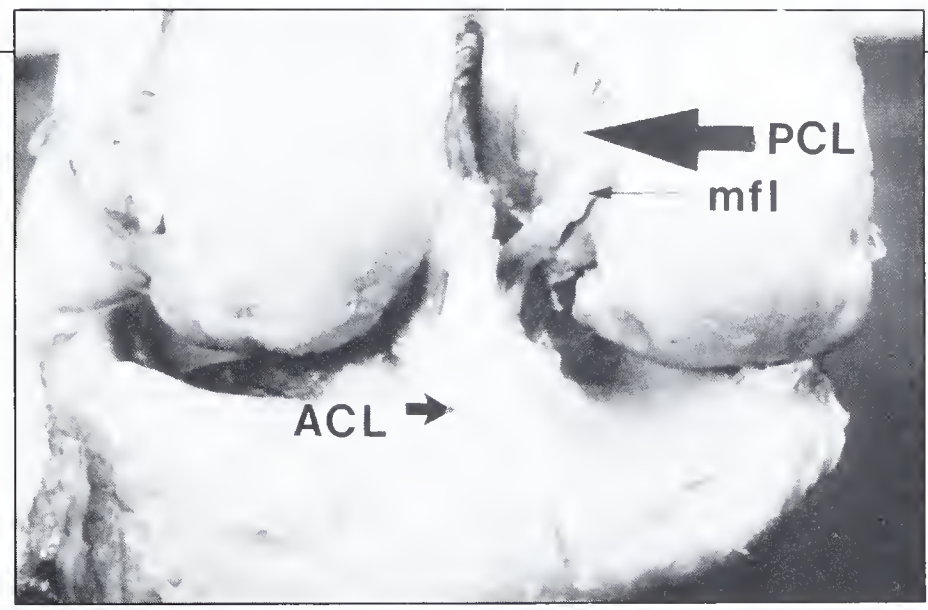


Figure 1: Anterior view of right knee showing gross anatomy of the cruciate ligaments. ACL - Anterior Cruciate Ligament, PCL - Posterior Cruciate Ligament, mfl - meniscal femoral ligament of Humphrey's.

Lachman test. This is an excellent test for ACL laxity. The knee is flexed 20° to 30° with one hand stabilizing the distal femur and the other applying an anterior force to the proximal tibia. The amount of anterior displacement should be estimated and the firmness of the end-point (ie. the point at which the forward displacement stops) should be assessed. The results of this assessment should be compared with the normal knee. Any perceived side-to-side difference is usually significant. The Lachman test can be graded as 1+ (0-5mm), 2+ (5-10mm), or 3+ (>10mm) with either a firm (normal), marginal, or soft end-point. If either is abnormal, the test is considered positive. Examiners appear to be better able to detect end-point differences than displacement differences. A soft, indistinct end-point suggests rupture of the ACL.

Anterior drawer. This is a more difficult and less reliable test for cruciate insufficiency in the acute setting. The knee is flexed to 90° and the foot is stabilized by having the examiner "sit" on it while the tibia is pulled forward using both hands. Anterior displacement is estimated and compared to that of the uninjured side by having the thumbs over the joint line and recording the amount of step off between the femoral condyle and tibial plateau. Again, any side-to-side difference is considered significant. It is essential that the hamstring muscles are as relaxed as possible since they often go into spasm or may be tight hence helping to stabilize any anterior displacement (ie. false negative). A false positive anterior drawer can be seen with a posterior cruciate ligament (PCL) injury when bringing the tibia from a subluxed to a reduced position. In addition, many normal knees have significant displacement in this position; hence, the importance of comparing both sides is again emphasized.

Pivot shift test. This dynamic test allows the examiner to gauge the degree of instability in a knee with an ACL injury. The examination is performed with the knee near full extension and slightly internally rotated. A valgus and anteriorly directed force is applied while the knee is brought into flexion. In early flexion, there is an anterior subluxation of the tibia but with further flexion (20 to 40 degrees), the posterior pull of the iliotibial band reduces the tibia posteriorly. This may recreate the feeling of instability in the patient with ACL deficiency. It is this relocation event (ie. as the tibia relocates posteriorly) that the examiner grades subjectively as 0 (absent), 1+ (pivot glide), 2+ (pivot shift), or 3+ (momentary locking).

Imaging

Imaging modalities used can include plain radiographs, bone scintigraphy, magnetic resonance imaging (MRI), arthrogram, and computerized tomography (CT).

Plain radiographs should be the first imaging study ordered to rule out other abnormalities and associated injuries[5]. Anteroposterior (AP) and lateral views of the knee provide good visualization of the tibiofemoral and tibiofibular joints. The skyline view allows assessment of the patellofemoral joint and provides an unobstructed view of the patella. An avulsion of the insertion of the ACL may be seen in the lateral or tunnel view. A vertically oriented Segond fracture (lateral capsular avulsion fragment) located posterior to Gerdy's tubercle (insertion site of the iliotibial band on the tibia) and superior and anterior to the fibular head is often associated with ACL injury. A PA flexion weight bearing radiograph can be used to evaluate any joint-space narrowing. Usually, clinical examination and plain radiographs are sufficient. Occasionally, however,

special tests may be necessary to evaluate the status of the ACL, meniscus or other associated pathologies that may be of prognostic value[5,6,17].

Bone Scintigraphy (or bone scan) is a nuclear imaging technique using technetium labelled phosphonates which is highly sensitive to areas of increased bone turnover. Therefore, it is more sensitive than X-rays which can only detect relatively extensive changes in bone composition. This technique can be used to detect radiologically silent, MRI demonstrated, subchondral bone infractions, as well as ligamental avulsions. Focal bone repair can occur in a variety of conditions seen in association with knee trauma. This has been demonstrated at the site of chronic meniscal tears presumably from local synovitis[14]. Bone scintigraphy has been used extensively to assess chronic knee pathology[15,16]. However, some authors have used bone scintigraphy to confirm osseous lesions seen on MRI in the acute ACL population[5,6].

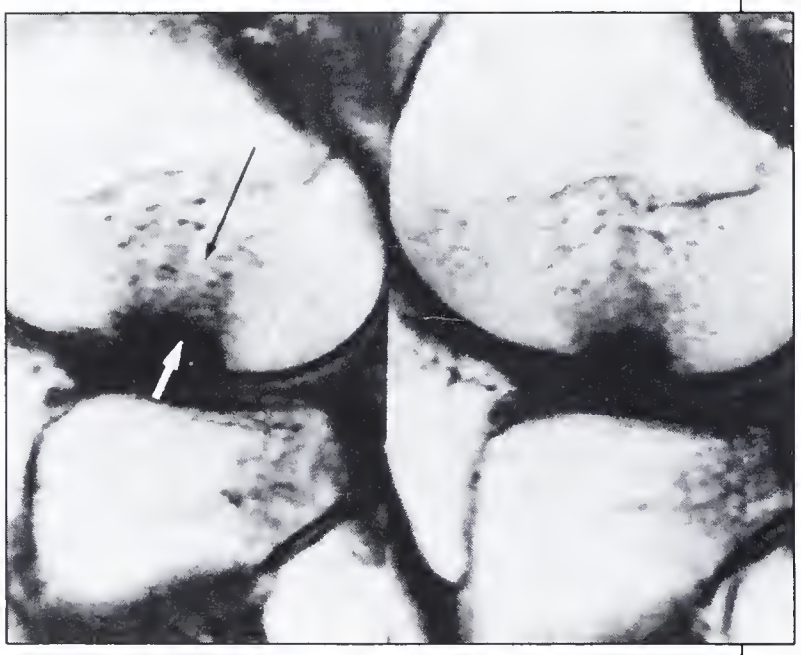


Figure 2: Sagittal magnetic resonance imaging section of a left acute ACL injured knee with a "bone bruise" or subcortical infraction in the lateral femoral condyle (arrows).

MRI is a non-invasive test which has a very high accuracy rate in assessing the ACL (approximately 95%). However, due to its cost and availability, MRI should not be used routinely since clinical examination and plain radiographs often suffice and are much less expensive. The normal ACL appears as a smooth, well defined, low intensity signal structure on a sagittal plane through the intercondylar notch. An abnormal ACL, however, shows discontinuity and possibly a wavy irregular contour of the anterior margin of the ACL indicating loss of tautness. Approximately 60 to 98% of ACL injuries have accompanying bone abnormalities not seen on normal radiographs[2,5,6,17,46]. These are subcortical fractures referred to as "bone bruises" (Figure 2). The significance and long term sequelae of these lesions have yet to be determined although they may play a part in degenerative changes in the ACL deficient knee[5,17].

The "ACL risk equation"[17] describes factors implicated in the pathogenesis of degenerative changes in the knee following ACL disruption. These factors may include degree of instability, subcortical infractions, meniscal damage, cytokine, growth factor levels, and other variables not yet fully elucidated. Traditionally, it is thought that chronic instability in ACL deficient knees leads to meniscal damage and subsequently puts the knee at increased risk of osteoarthritic changes at an earlier age, hence the reasoning to reconstruct the ACL. However, Dye et al.[18] (1994) recently showed that many patients demonstrate degenerative changes despite restoration of normal laxity parameters following ACL reconstruction. A study conducted by Fritschy et al.[8] (1990) actually demonstrated a higher incidence of joint arthrosis on bone scan and radiography in reconstructed knees versus those not reconstructed. Fu et al.[19] (1994) found that chronic elevations of cartilage catabolic cytokines without corresponding elevations in protective antagonists in the chronic ACL deficient knee may be responsible for the degenerative joint disease following ACL reconstruction. Hence, this is a contentious issue at the moment which will become clearer in the future as the ACL risk equation is further defined.

CT and arthrography are of minimal use in evaluating ACL deficient knees. The role of arthrography is limited mainly to the evaluation of the status of the menisci since interpretation of the ACL is operator-dependent and may be misleading if the synovial sheath surrounding the ACL is intact.

Other Special Investigations

Instrumental ligament testing devices such as the KT-1000 arthrometer is used for precise and accurate measurement of anteroposterior displacement. In a unilaterally injured knee, a side-to-side difference of 3mm or greater is classified as pathologic. These devices can be used preoperatively, intraoperatively, and postoperatively. When the integrity of the ACL and menisci remains in doubt, examination under anesthesia when the patient is completely relaxed, may demonstrate ligamentous laxity not evident when the patient is conscious. However, one may still see a false negative clinical examination if there is a displaced bucket handle meniscal tear or a stump of the ACL impinging in the intercondylar notch. The persistently locked knee is an indication for arthroscopy which can be used to evaluate the ACL, menisci, and other intra-articular joint structures. If meniscal pathology is noted, repair or excision can be performed at that time. If an ACL stump is causing a mechanical block to knee motion, it can also be attended to arthroscopically. In general, however, reconstruction of the ACL is delayed until the acute inflammation has settled and full range of motion is attained.

Treatment

Although the ACL has been one of the most extensively studied ligaments in the body, there is still no ideal method of therapy which can restore the normal biologic,

physiologic, and mechanical characteristics of the ligament in the ACL deficient knee. The decision of whether to reconstruct or treat conservatively depends on various factors unique to each case. Variables to consider include the following: associated pathology, patient age, level of activity, degree of instability, type of injury to the ACL, patient compliance, and whether the injury is acute or chronic.

The presence or absence of other associated pathology or injury involving the knee needs to be considered prior to a treatment decision. Noyes and McGinnis[20] (1985) suggest that one criterion in favour of reconstruction occurs when an acute meniscal repair is required and the added stability provided by a repaired ACL is judged to be beneficial in preventing further meniscal damage. Evidence of joint space narrowing and degenerative changes in a chronic ACL deficient knee must also be considered. In those patients suffering from medial joint line pain without associated instability, a high tibial osteotomy (a surgical realignment of the knee joint by excision of a wedge of bone from the proximal tibia), used to unload the affected (medial) compartment, may be more appropriate than reconstruction of the ACL[43].

Patient factors such as age, level of activity, and compliance with rehabilitative therapy need to be taken into consideration as well. In a younger skeletally immature patient with open growth plates, conservative therapy should be attempted initially. This is due to the possible risk of growth arrest of the affected limb in surgical procedures requiring drilling tunnels across the plate[21].

Patients involved with activities requiring jumping, pivoting, cutting, lateral motion, sudden acceleration-deceleration (ie. "high-risk sports"), are at increased risk of further injury or re-injury to their knee. Many patients treated non-operatively are unable to participate fully in such activities.

Rehabilitation is crucial in determining the successful outcome of the surgical procedure[26,41,42]. There would be no sense going through a surgical ligament reconstruction if the patient is unwilling or is unable to participate in an extensive rehabilitation program post-operatively.

The degree of instability, pain, swelling and functional impairment a patient experiences needs to be factored into a treatment plan. Surgical reconstruction is considered in the patient who is unable to compensate without an ACL. These patients usually present with instability followed by swelling, pain, and functional disability affecting their ability to participate in sports, work, or other activities of which restrictions would be intolerable to the patient[44].

Not all ACL injuries need to be surgically reconstructed. Ligamentous injuries can be graded as type I (stretched), II (partial tear with good end-point), or III (complete rupture with poor end-point). Conservative therapy is indicated in type I and II injuries. Type III injuries, however, will not heal on their own and may require surgical correction depending on the other factors listed.

Finally, the timing of the original injury (ie. acute vs. chronic) needs to be considered. Noyes and McGinnis[20] (1985) described their "rule of thirds" with regards to conservative management in acute ACL injuries: one-third of the patients will compensate adequately and be able to pursue recreational activities, one-third would be able to compensate but will have to give up significant activities and one-third will do poorly and will need future reconstructive surgery. From a surgical point of view, authors[22,23,24] to date report mixed results after repair of the acutely torn ACL with early primary suturing procedures. Odensten et al.[25] (1985) concluded that early primary suturing with augmentation may give patients with an acute ACL tear a better start than conservative therapy. As shown by the diversity of these results, opinions concerning the treatment of the acutely torn ACL clearly vary. Currently, the primary indications for surgery in an acute injury is anterolateral rotatory instability in an active individual who is unwilling to modify sports participation. Reconstruction in these individuals is performed only after full range of motion is restored post-injury.

In chronic injuries, one must evaluate if the instability is causing functional disability and if the patient is at risk of developing meniscal damage with subsequent joint cartilage degeneration[46]. However, whether fixing the ACL surgically will decrease the incidence of joint deterioration is a contentious issue presently.[8]

Two factors found to be most predictive of those needing later surgery are as follows. The first is the number of hours per year of high-risk sports the patient participated in prior to injury. The second factor is the maximum displacement difference between the normal and abnormal knee as measured by instrument ligament testing. It was found that patients with a 7mm or greater side-to-side difference with more than 50 hours of high-risk sports activity were in the high-risk group.

Conservative therapy in ACL injured knees includes patient education regarding high-risk activities and preventative measures to avoid recurrent injuries, specialized exercises and stretches (to help increase range of motion, strengthen, and stabilize the joint), effective pain control, activity modification, and possibly bracing.

The initial conservative treatment goal of the acutely injured ACL is to provide comfort and eventually obtain full range of motion. This is achieved through splinting with or without crutches, a non-steroidal anti-inflammatory drug (NSAID), and early active range of motion. Strengthening of the quadriceps and hamstrings is achieved with closed-chain weight-bearing exercises (as opposed to open-chain, leg extension type exercises which may put excess stresses upon the articular surfaces in an ACL deficient knee). In some patients who have lost their ability to recruit their leg muscles in the correct order, pulsed electrical muscle stimulation may be of help.

The role of derotational bracing remains controversial but the fact is that some patients feel they have better function in a brace which allows them to increase their level of activity and may increase or facilitate their proprioceptive function. However, the use of braces cannot

be substituted for strengthening exercises and it cannot assure absolute protection in those patients with gross instability who choose to participate in high-demand activities.

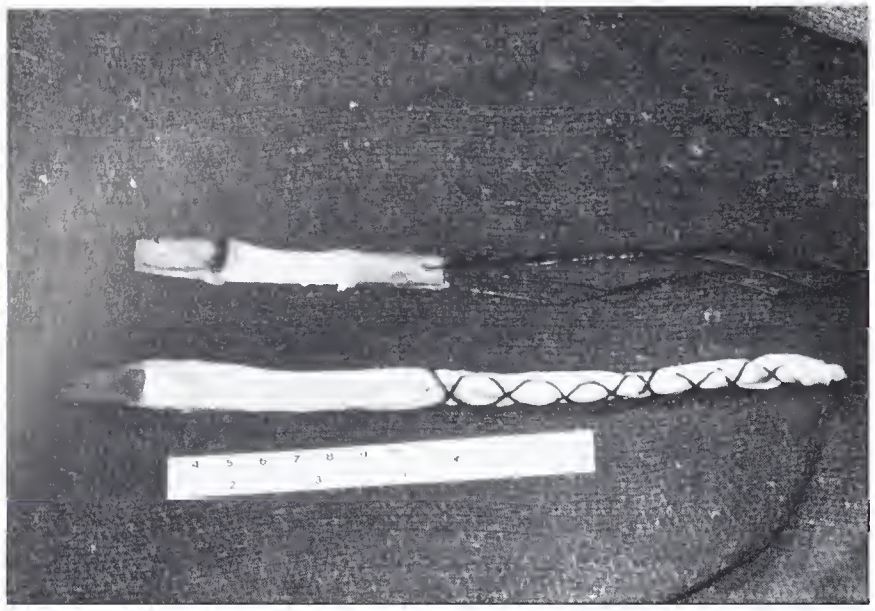


Figure 3: Prepared allografts are illustrated with a bone-patellar tendon-bone graft (top) and an achilles tendon graft (bottom).

Operative management for intra- and extra-articular reconstruction of the ACL have included various autogenous grafts (eg. iliotibial band, semitendinosus and gracilis tendons, patellar tendon, quadriceps tendon), allografts (eg. achilles tendon, patellar tendon) (Figure 3), and synthetic materials (eg. Goretex, Dacron). The majority of ACL reconstructions are intra-articular so as to mimic the normal anatomy and function of the ligament. Extra-articular reconstructions do not provide the same degree of restraint as provided by a well-done, intra-articular reconstruction in active individuals[27].

Studies have shown that both autografts and allografts undergo similar biologic and biomaterial remodelling albeit the allograft remodels at a slower rate. To make the allograft less antigenic, deep-freezing and freeze-drying have been used and they did not appear to alter the biomaterial properties of the graft. However, one study has shown that a significant number of allograft ACL reconstructions develop a delayed immune response by 6 months post-operatively[28]. In addition, secondary methods of sterilization to treat the graft for bacterial and viral contamination such as with ethylene oxide and gamma radiation, have been associated with alterations in graft properties. The main advantage with an allograft is the lack of donor-site morbidity associated with using a part of one's own normal anatomy to repair the defect. Nonetheless, there is little evidence at this time that the long-term results are better than those associated with autogenous tissues[29]. Another factor to consider is the availability and quality of allograft tissues[45]. Hence, most surgeons reserve the use of allografts to those with a failed previous ACL reconstruction and/or difficulty in obtaining autogenous tissue due to size or increased risk of donor-site morbidity (eg. multiple-ligament injured knees).

Synthetic ligaments have been utilized with generally poor results[30]. The most common complication was that of subsequent graft rupture, particularly in active individuals because synthetic grafts do not possess the same biomechanical properties as autogenous tissue and hence do not undergo the same remodelling processes. Another problem found in in-vivo and in-vitro studies was that of synthetic graft particles inducing an inflammatory response which promotes episodes of both acute synovitis or long term osteoarthritis of the knee[31]. Because of all these complications, prosthetic replacement of the ACL is not recommended.

The ligament augmentation device (LAD), used in addition to autogenous tissue, has been used as a method of increasing the initial tensile strength of the graft, as an enhancement of fixation, and as a means of providing extra length when needed. The theory is that the stiffer LAD will carry most of the load during the early postoperative phases at which time the tensile strength of the autogenous tissue is compromised as it revascularizes and new collagen forms[32]. However, the cost of the LAD along with the reported results showing no clear advantage suggests that their use be restricted to specific indications such as in the presence of weak or inadequate tissue or the need for enhancement of length or fixation.

Autogenous tissue grafts still remain as the first choice when reconstructing the ACL[47]. Factors considered in autograft selection include the following:

Biomechanical properties of the graft. Noyes et al.[33] (1984) examined the biomechanical properties of nine different autograft tissues and found that a bone-patellar tendon-bone complex (BTB) was approximately 1.6 times as strong as the normal human ACL. The semitendinosus (ST) was 70%; the gracilis (GC), 50%; the distal iliotibial band (ITB), 50%; and the quadriceps-patellar retinaculum-patellar tendon complex, 14-21%. Other studies have shown that multiple strands of ST or ST-GC composites are stronger than a normal ACL. However, these studies do not take into account subsequent remodelling of the graft once put in place. Autogenous tissue grafts merely provide a collagen lattice in the early stages of graft resorption, revascularization, and restructuring with new collagen. Studies have shown that collagen tissue produced after ACL reconstruction does not match the size or density of normal ACL collagen fibers[34]. Hence, the exact long term strength of these grafts has yet to be determined. Surgeons vary in their preference of autogenous tissue. Internationally, the BTB graft has been widely accepted and used in ACL reconstruction because of its greater initial tensile strength, greater bulk, and more secure bone-to-bone fixation. Others prefer using the ST which is often double-looped, used in conjunction with the GC, or even quadruple-looped[35]. Advantages to using the ST include greater elasticity and it requires smaller drill holes for insertion. It is also easier to harvest and carries less risk of donor-site morbidity (eg. patellofemoral pain). Still others prefer using the ITB in what is called a lateral substitution over the top

Figure 4: A lateral radiograph of the knee demonstrates the interference fixation of the tibial and femoral bone blocks after ACL reconstruction with a bone-patellar tendon-bone (BTB) graft. (See Fig. 5 for close-up illustration).

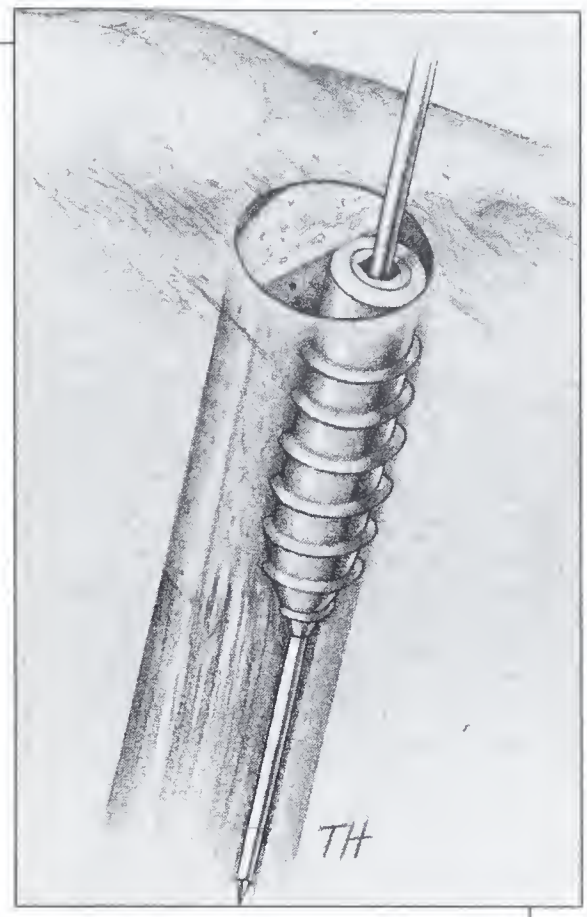


Figure 5: Illustration of interference fixation of the bone block in a BTB graft into the prepared tunnel with an interference screw.

(LSOT) procedure which provides both intra-articular and extra-articular stabilization. However, this technique requires a larger incision, an excellent understanding of the anatomy of the knee with, in general, poorer results as reported in the literature[27]. There are many variations in surgical techniques using these autogenous grafts but because of the current international acceptance of the BTB technique, the rest of this review will primarily focus on the surgical issues related to graft harvestation, fixation, donor site morbidity, complications and individual patient considerations in terms of the BTB technique.

The ease of graft harvest. The BTB is probably the most time consuming and labour intensive in terms of harvesting if done early in the learning curve (ie. it is technically demanding especially to those inexperienced with the procedure).

Security of graft fixation. The weak link in the reconstructed knee in the early post-operative period is the point of ligament or graft fixation. Studies seem to indicate that BTB with bone-to-bone fixation (Figure 4 and 5) offers the most tensile strength in comparison to other techniques utilizing soft-tissue fixation to bone[6].

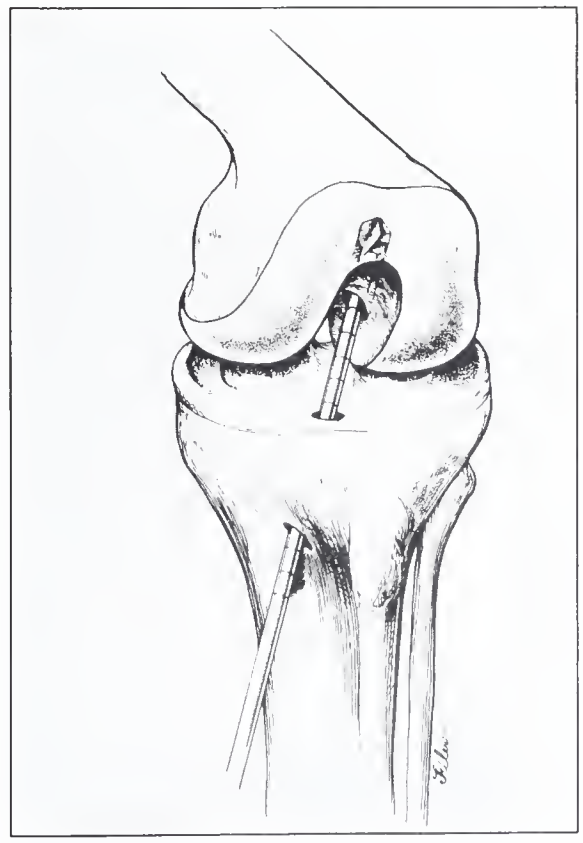


Figure 6: Illustration of proper tunnel placement for a BTB graft. Arthroscopic ACL reconstruction can be performed with one incision if one drills the femoral tunnel by passing the reamer through the tibial tunnel.

Potential donor site morbidity. BTB harvests have resulted in rare cases of patellar fracture, avulsion of the inferior pole of the patella, and patella tendon rupture. Several studies have also shown that even with modern rehabilitation protocols, the incidence of anterior knee pain and patellofemoral morbidity is higher in those receiving BTB autografts. Patellar baja (low riding patella) has also been documented in cases of BTB where the patella tendon defect was sutured after the graft was harvested.

Individual patient considerations. BTB may not be the graft of choice in those with a history of patellar tendinitis or patellofemoral pain. The finding of a short or narrow patella tendon may also exclude BTB as being the first choice. A previous pes anserinus (distal tibial insertion site of the sartorius, gracillis, and semitendinosus tendons) transplant or inadequate size of the hamstring tendons may negate the hamstring source of graft material.

Appropriate surgical technique is very important in obtaining proper function of the reconstructed ACL. It is of utmost importance that the graft be positioned as near an anatomic position as possible to provide stability and a full range of motion without any impingement[36]. This can be achieved either arthroscopically[37,38] or through an open procedure. Proper graft tensioning is also important in achieving a successful ACL reconstruction and should be checked intraoperatively in different positions of knee flexion and extension.

Complications of ACL Surgery

Complications may be encountered with the various approaches to reconstruction of the ACL[39,40]. Early complications may include anesthetic morbidity, vascular or neurologic injury, deep vein thrombosis,

infection, fluid extravasation, and compartment syndrome. Late complications include decreased range of motion, residual laxity, quadriceps weakness, patellofemoral pain, and reflex sympathetic dystrophy. There may be complications associated with graft donor site morbidity, impingement and failure. Tunnel preparation (Figure 6) may demonstrate errors in placement and posterior wall "blow-out" (drilling too far in on the femoral side). Other complications include persistent effusion, growth plate injury, patellar tendon rupture and patella fracture. Flexion contracture, joint stiffness, quadriceps atrophy, and patellar irritability are the most frequent problems encountered after ACL reconstruction; hence, the importance of starting an early aggressive rehabilitation program is emphasized. Recent emphasis on the use of allograft tissue can also be associated with potential problems such as risk of disease transmission, lack of structural integrity, possible effects of secondary sterilization, immunogenicity of grafts, and healing potential.

Rehabilitation

Shelbourne and Nitz[41,42] have advocated an accelerated rehabilitation protocol. The objective is to maintain full knee extension as much as possible as compared to that of the normal knee. This protocol is based on the BTB graft method but the principles are similar with other grafts as well. While range of motion is gained and maintained, exercises to increase strength and agility are slowly introduced which is best achieved by closed-chain weight-bearing exercises (eg. leg presses, squats, lunges etc). Proprioceptive drills involving balance are also important in regaining full function of the affected knee.

Summary

As can be seen, the management of ACL injuries is complex and continuously evolving. Many factors come into play in deciding who is a surgical candidate versus those that can be treated conservatively. The ultimate goals of reconstructive surgery are to improve knee stability so that the patient can function as normally as possible, to prevent meniscal damage, and to possibly decrease the risk of future joint articular cartilage degenerative changes. Primary candidates for ACL reconstructive surgery include: 1) Those patients with an acute injury who have an active lifestyle they refuse to modify. Reconstruction is performed in these individuals only after full range of motion is restored. 2) Those with a chronic ACL deficiency that results in functional instability. Autogenous tissue grafts are preferred in reconstructive surgery of the ACL. Although many different autogenous grafts have been advocated, the BTB graft technique is currently receiving wide spread popularity internationally due to its greater initial tensile strength, greater bulk, and more secure bone-to-bone fixation. However, it should be pointed out that no surgical technique can fully restore the anatomy and function of a normal ACL. The answers to many questions remain to be found in carefully designed, prospective, randomized, long-term outcome studies comparing the different techniques of treatment.

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The Challenge of Clinical Breast Examination

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Abstract

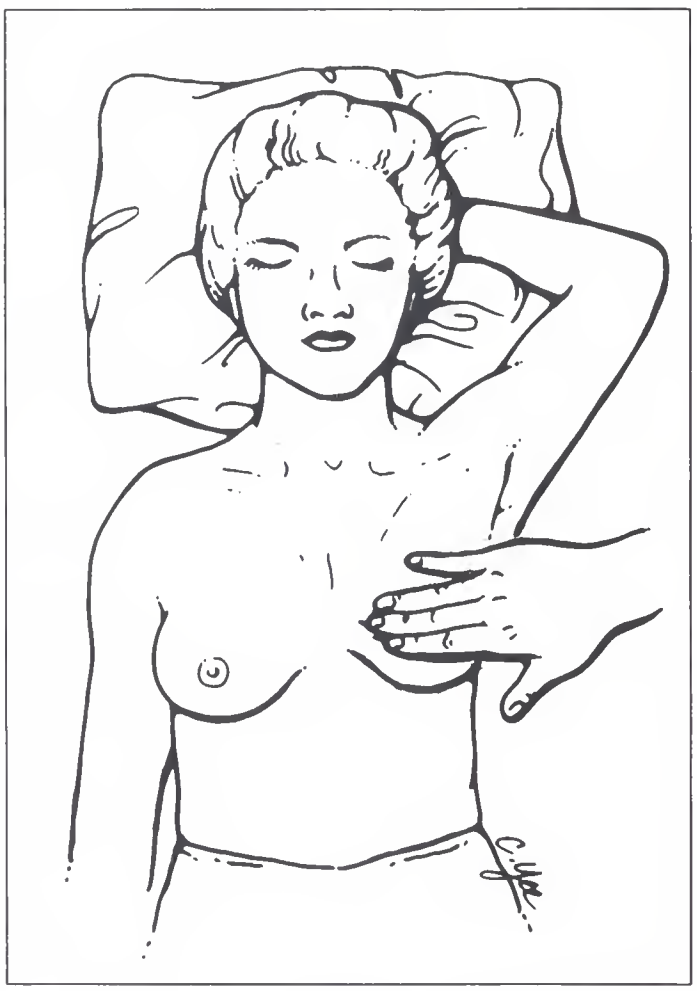
Examination of the female breast is an important component of the physical examination because of the high incidence of disease in this organ. In this report we describe a proper examination of the breast. Two techniques of palpation, the *Vertical Strip Method* and the *Radial Vector Method* are presented. A description of the findings in malignant and benign conditions of the breast is also included to aid the examiner with the diagnosis. Mammography is the most important technique in the detection of clinically occult breast lesions. Included in this article are a description of mammography and some of the more common questions asked by women with respect to this technique.

Introduction

Well-performed, thorough and consistent examination of the female breast is a requisite skill for all medical trainees in order for them to deliver state-of-the-art care.

Breast complaints form a relevant and substantial problem in the primary care setting. A recent survey of Ontario family physicians suggested that up to 15% of patients in their reproductive years require follow-up for breast complaints.[1] While doctors are expected to deliver messages related to disease prevention and health promotion, in many instances, women attend their family physicians only for specific assessments when ill, and do not avail themselves of the periodic health assessment. In addition, when women visit their family doctors, they do not appreciate the need for, nor do the physicians always do a thorough breast examination.

The gap that exists is two fold. Firstly, breast health is not yet part of our consciousness. Women, following instruction from their physicians, should be competent at performing a regular breast self-examination, they must attend for regular clinical breast examination, and they must understand and participate in screening for breast cancer when it is appropriate. Secondly, clinical examination of the breast must be performed consistently and well. It is clear that for providers to be adequately prepared to deal with breast problems in practice, they must have:



CYNTHIA YEE

1) an adequate body of knowledge;

2) skills at history taking and doing clinical breast examination; and

3) an appreciation of the application of their knowledge and skill in the practice setting.

In this report we describe the requisite knowledge that a health provider requires to take a comprehensive and appropriate history and to perform a structured and complete clinical breast examination. Two examination techniques, the *Vertical Strip Method* and the *Radial Vector Method*, are presented in detail. Since an implicit part of the examination involves teaching breast self-examination to women, a brief description of this is also included.

Requisite Knowledge of Breast Disease

The understanding of breast disease includes knowledge of the normal anatomy, variants of normal, and normal physiology of the breast. A description of this knowledge is beyond the scope of this article and the reader is encouraged to refer to regular anatomy and physiology textbooks.

Relevance and Epidemiology of Breast Disease

It should be remembered that breast cancer is a potentially life threatening disease. It is a significant disease in our

society, accounting for the most common site of malignancy in women, and a significant cause of mortality. In Ontario this year, 6500 new cases of breast cancer are expected to be diagnosed, and 2100 women will die from this disease. The incidence of breast cancer increases with age. Seventy five percent of all breast cancer cases are diagnosed in women over the age of 50.

Benign Breast Complaints

Many women visit their primary care physician for a breast complaint at some time during their lives. Some common conditions seen in young women are fibroadenomas (both solitary and multiple), mastalgia, complaints of breast lumpiness related to an underlying fibrocystic condition, nipple discharge, and complaints related to breast feeding and lactation.

Signs and Symptoms of Breast Cancer

Clinical signs and symptoms of breast cancer must be well understood. In the past, diagnosis of breast cancer usually occurred because a woman found a lump in her breast. Increasingly, we see the diagnosis result from a screen-detected abnormality or a mammographic finding. The most common signs and symptoms of breast cancer are listed in Table 1.

Diagnostic Workup

A full understanding of the tools in the diagnostic armamentarium is necessary. Film-screen mammography, interpreted by those with specific expertise, should become the norm. Mammographic abnormalities can often be characterized by extra views with cone-compression or magnification features. Ultrasound, while not a good population screening tool, functions well in the discrimination between cystic and solid lesions, regardless of whether they are felt on clinical breast examination or identified on mammography. Fine needle aspiration, core biopsy under mammographic or ultrasound control, needle localization biopsy, and open biopsy, all have relevance in appropriate circumstances.

Table 1

Signs & Symptoms of Breast Cancer*

Palpable mass
Mammography abnormality
Breast swelling and pain
Skin dimpling, edema, erythema
Nipple discharge, retraction or ulceration
Axillary lump

**These signs and symptoms represent early disease; adapted from Bland and Copeland* [2]

Screening for Breast Cancer

There has been clear-cut evidence in the last ten years that screening for breast cancer in women aged 50-69 decreases mortality from this disease.[3] For this reason, countries with a high natural incidence of this disease have undertaken screening programs, and, indeed, in Canada, many provinces now support this activity. In 1989, the Ontario Breast Screening Program was funded. Currently, this service is offered through ten dedicated screening centers in the province. All Ontario women over the age of 50 should be participating in regular screening for breast cancer.

Mammography

State-of-the-art film *screen mammography* is the most important technique for the detection of clinically occult (nonpalpable) breast lesions.[4] Most palpable breast cancers measure 2cm or greater in diameter. Mammography has the capability of detecting cancer often in the early malignant phase when lesions are small (before they reach 0.5cm in diameter) and when outcome is extremely favourable. Early detection programs of population screening in women over the age of 50 result in reduced mortality. This has been consistently shown in international studies and forms the basis for the breast screening programs in this country.

Diagnostic mammography is an important tool in the investigation of significant breast findings. This may involve extended views such as magnification or cone compression to better characterize abnormal findings. Workup may involve coordinating mammographic findings with ultrasound. Mammography is usually not done in women under 30 as the examination is of limited value in young dense breasts and there is no wish to expose young women unnecessarily to diagnostic radiation.

According to the Ontario Breast Screening Program most women having mammography have a number of questions. The most common questions are presented on Table 2.[5]

The Breast Self-Examination

Greater than 85% of of breast lumps are first discovered by the patient.[2] Therefore the breast self-examination (BSE) is an important skill for women to acquire with potential to detect breast cancer at an earlier and more curable stage. Unfortunately, a substantial number of women have never performed BSE.[6] In addition, many of the women who consistently perform BSE do it incorrectly. Generally, there is no accepted right age to begin BSE. Premenopausal women should perform the examination about a week after the beginning of each menstrual cycle. Postmenopausal women should be instructed to perform the examination on the same day each month. The technique of "first you look, then you feel" as described by Allan Bassett is recommended.[7] A physician should teach the BSE technique to the patient at the completion of the clinical breast exam (see cut-away section).

Table 2

Common Mammography Questions Answered

What is mammography?
Mammography is a simple low dose x-ray picture of the breast. It is used to detect breast cancer in its earliest stages, before a lump can be felt, and when treatment can be most successful.

Is there much risk from radiation?
Modern mammography equipment produces *extremely low* amount of radiation. From a risk standpoint, the risk of having a mammogram is as low as traveling 400 miles by air, driving 60 miles by car, or smoking 3/4 of a cigarette.

How do I prepare for a mammogram?
To get the best possible image of the breast:
• It is best not to use deodorant or body powder containing talc before having a mammogram otherwise you may be asked to wash your underarms and breasts.
• Since you will be undressing above the waist for the examination, it is best to wear clothing that can be removed easily
• At the time of the appointment, the nurse examiner will describe the mammography procedure

What will happen in the exam?
You will first be asked to undress above the waist and put on a gown. The mammography technologist will position you at the machine —usually standing. During the examination, your breast is pressed between 2 plastic plates. Two views of each breast will be taken as part of screening mammography. You may be asked to wait until the film is developed to be sure the pictures are of good quality.

Does a mammogram hurt?
To get a clear picture, compression of the breasts is necessary. Some women may feel a little discomfort, but the exam takes only a few minutes. It is wise to avoid having a mammogram done during the premenstrual period if your breasts are tender at that time.

What will the results mean?
The mammogram results will be read by a radiologist. Most women will receive normal results. It is important for you to know that an abnormal result does not necessarily mean breast cancer is present. If the radiologist does detect an abnormality, you and your physician will be notified that further assessment is necessary.

Techniques of Examination

General Approach

It is important to elicit a full history, not only as a first step toward making a diagnosis but also to establish communication with the patient and appreciate the level of her anxiety. It is helpful to ask the patient whether she has noted anything abnormal with her breasts. Physiological changes of the breast should not be confused with pathological changes. The commonest symptoms in breast disease include lumps, pain, tenderness, nipple discharge, skin changes and size or shape changes. Details relating to any of these changes should be sought along with information about general health, previous breast disease, reproductive history and family history. Although the etiology of breast cancer is not yet known, epidemiological data suggest that genetic, environmental and endocrine factors may contribute to its initiation and promotion.[8] In addition, the age of a patient with a palpable breast mass is important in determining the probable pathology. For example, the incidence of breast cancer increases sharply above the age of 40. The main risk factors associated with breast cancer are listed in Table 3.

A careful and structured physical examination of the breasts may require at least 3-5 minutes. Before beginning tell the patient that you are going to examine her breasts. An adequate inspection requires that the patient be disrobed to the waist. Gentleness and courtesy with attention to the patient as a person and a composed approach will reassure the patient of your regard for her sensitivity and will help her to relax.

Examination in the Upright Position

I. INSPECTION

A. Patient Sitting with Arms Down

Visual inspection in the upright position under good lighting conditions is the first step in the physical examination of the breast. The patient should be in a sitting position facing the examiner, with her arms relaxed and hands resting on the thighs (Figure 1a).

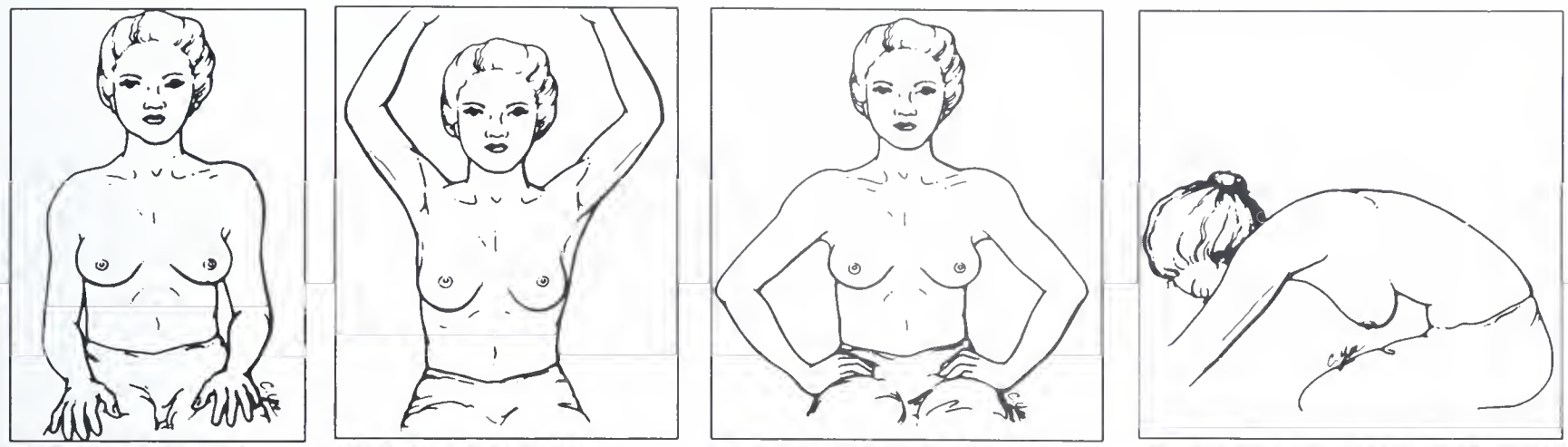
Table 3

Risk Factors Associated with Breast Cancer*

- Increasing age
- Familial history of breast cancer
  - 70% of women with breast cancer have no specific family history
  - 1st degree female relatives have a slightly increased risk
  - appr. 5% of women with breast cancer have Hereditary Breast Cancer
- Premalignant breast lesions
  - atypical epithelial hyperplasia
  - multiple papillomatosis
- Personal history of breast cancer
- Age at first birth (>30 yr)
- Previous exposure to high dose radiation to the chest
- Early menarche (<12 yr)
- Late menopause (>55 yr)
- Nulliparity
- Obesity
- Excess dietary fat
- High alcohol consumption

**Adapted from references 2 and 8*

Figure 1: Positioning of the patient during the visual inspection of the breasts



a) Patient sitting with arms down

b) Patient sitting with arms raised

c) Patient sitting with hands pressing hips

d) Patient sitting and leaning forward

Inspect each breast. (Figure 2) Note:

1. Size and symmetry

Although a difference in the size of the breasts is not abnormal, in some cases it may denote a congenital anomaly, cyst formation, inflammation or tumour.

2. Change in contour

Look for abnormal bulging, or signs of skin retraction such as flattening of a lateral contour or dimpling. Retractions signify the abnormal traction on the suspensory ligaments that occurs with carcinoma.

3. Superficial appearance

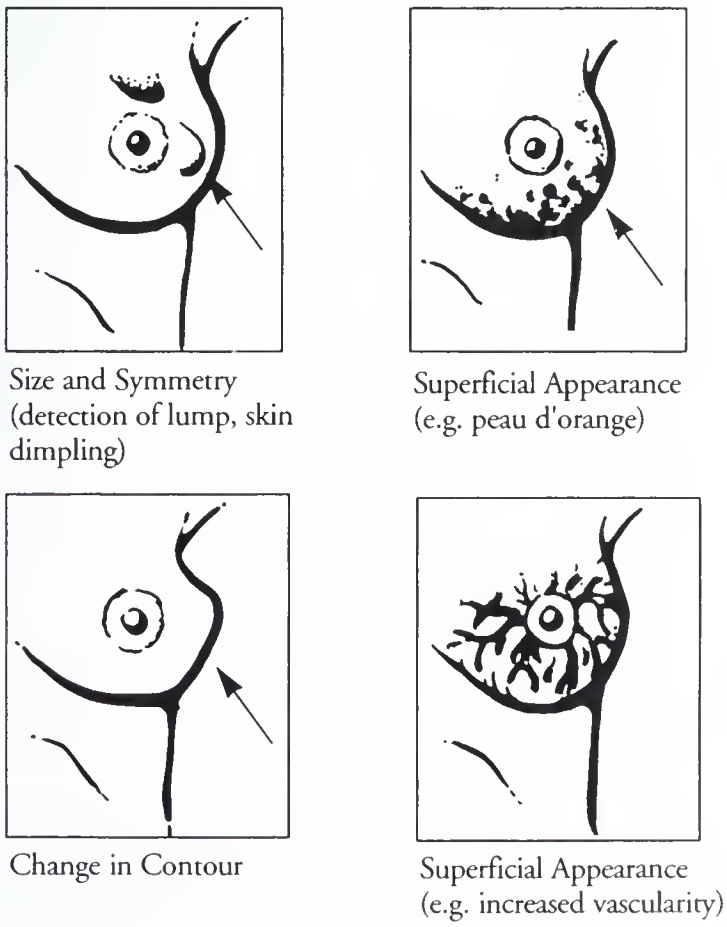
Erythema may be associated with inflammation due to an infection or it may indicate a local reaction of the skin to an invasive cancer, a condition known as *inflammatory breast carcinoma.*

Edema is produced by lymphatic obstruction and is manifested by a "peau d'orange" (orange peel) appearance of the skin. The sweat gland openings are visualized as deep pits surrounded by edematous skin. Notation should be made as to the exact location of the skin changes. The breast may have a similar appearance after radiation therapy.

Abnormal vascularity on the surface of the breast may indicate accessory blood supply of a neoplasm.

Figure 2: Inspection of the breast and areolae

Figure 2a: Inspection of the breast



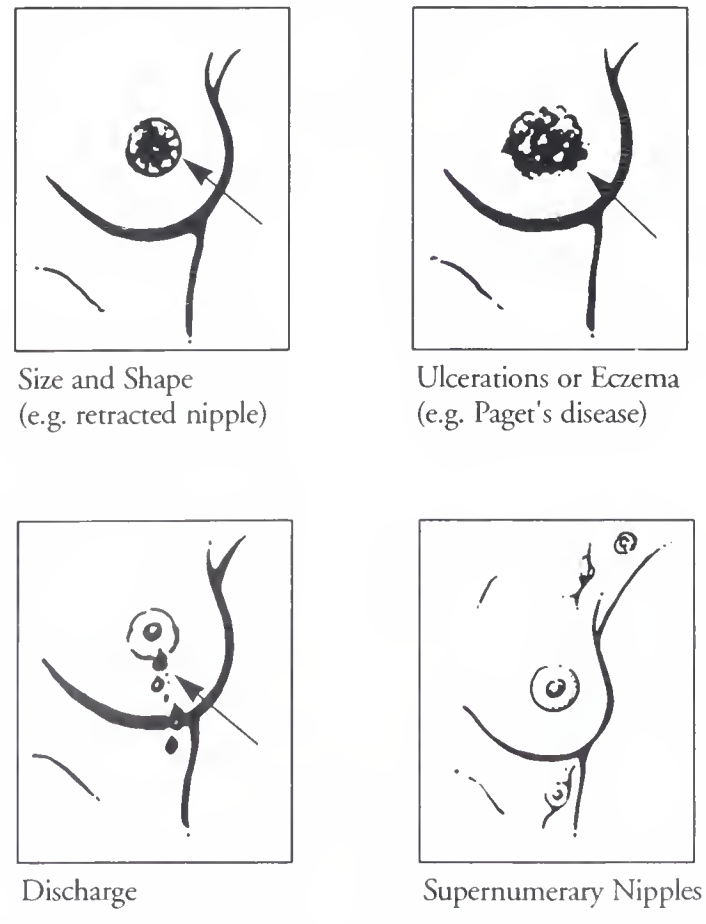
Size and Symmetry (detection of lump, skin dimpling)

Superficial Appearance (e.g. peau d'orange)

Change in Contour

Superficial Appearance (e.g. increased vascularity)

Figure 2b: Inspection of the areolae and nipples



Size and Shape (e.g. retracted nipple)

Ulcerations or Eczema (e.g. Paget's disease)

Discharge

Supernumerary Nipples

Inspect the areolae and nipples (Figure 2). Note:

1. Size and shape

Slight asymmetry in the areolae or nipples is not uncommon.

Inversion of one or both nipples may be a developmental anomaly and is not uncommon. But recent unilateral retraction or inversion of a previously erect nipple may be a consequence of shortening of the suspensory ligaments by an underlying tumour or inflammatory process.

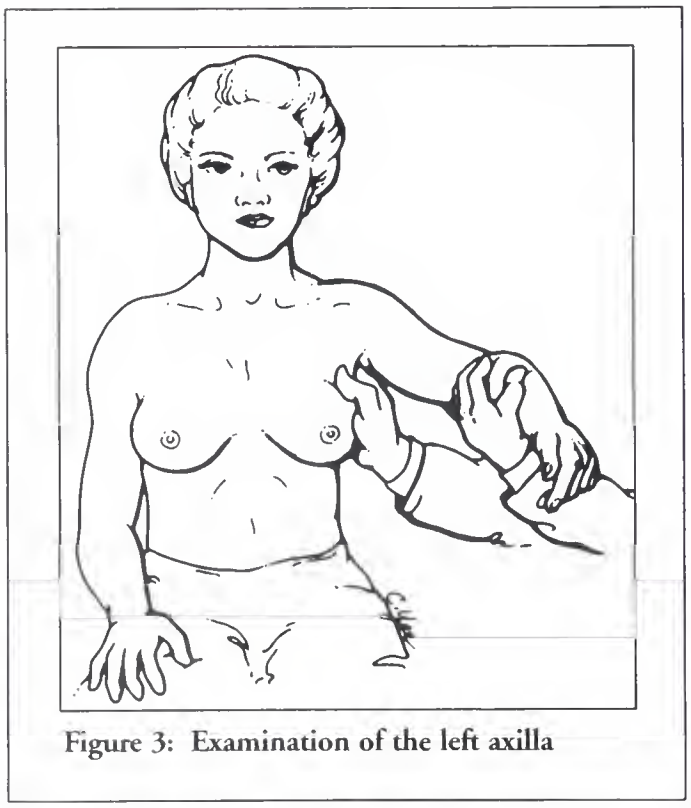


Figure 3: Examination of the left axilla

2. Ulcerations or eczema

Rough thickening or ulceration of the nipple which may have spread to the adjacent areola may indicate a malignant process of the breast (Paget's disease).

3. Discharge

Serous, bloody, amber or opalescent discharge appearing at the nipple should be noted. A spontaneous, unilateral discharge should increase the examiners suspicion of a pathological condition.

4. Supernumerary nipples

These appear as one or more nipples along the 'milk line' and are found most commonly in the axilla and below a normal breast. They are not associated with breast disease.

B. Patient Sitting With Arms Raised

Have the patient raise her arms over her head to increase the tension of the suspensory ligaments (Figure 1b). This will accentuate any suspected skin dimpling. Look for a shift in the relative position of the nipples (the nipple usually deviates or points toward the cancer), and any variations in the contour or symmetry of the breasts. In women with large breasts inspect the inferior surfaces by elevating each breast.

C. Patient Sitting with Hands Pressing Hips

Have the patient press her hands against her hips to contract the pectoral muscles (Figure 1c). This will also exaggerate dimpling and reveal deviations in contour or symmetry.

D. Patient Sitting and Leaning Forward

Ask the patient to lean forward from the waist (Figure 1d). This maneuver is helpful in inspecting the contour and symmetry of large or pendulous breasts since leaning forward allows them to hang freely away from the chest wall.

II. EXAMINATION OF THE SUPRACLAVICULAR FOSSAE AND AXILLAE

Lymphatic drainage of the breasts is of great clinical importance in the spread of breast cancer. Therefore thorough examination of the breasts must include examination of the regional lymph nodes. Special attention should be paid to three groups of nodes: The axillary nodes, the supraclavicular nodes and the infraclavicular nodes. For each of these note the size, location, consistency and mobility.

Begin by palpating the supraclavicular and infraclavicular areas. This is best carried out with the patient in the sitting position.

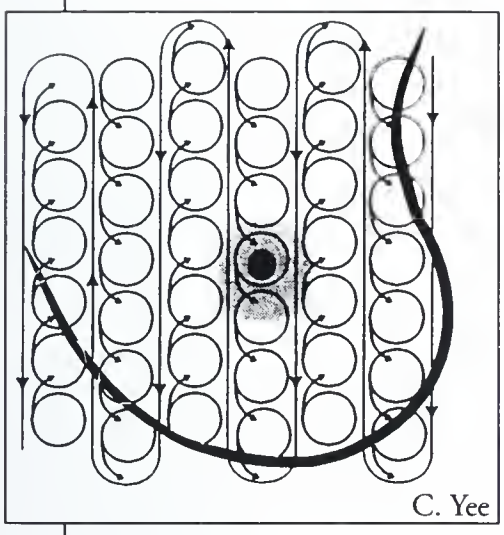
Next palpate the axillae. To palpate the left axilla ask the patient to partly abduct her left arm. Support the patient's left lower arm with your left hand while palpating the left axilla with your right hand as shown in Figure 3. With the pads of your fingertips reach deep into the axilla, pushing firmly but not aggressively. Your fingers should be directly behind the pectoral muscles pointing towards the midclavicle. Then try to feel the lymph nodes by sliding your fingers inferiorly while making small rotary motions. Be sure to explore all sections of the axilla. Then, reverse this procedure to examine the right axilla with your left hand.

III. PALPATION OF THE BREASTS

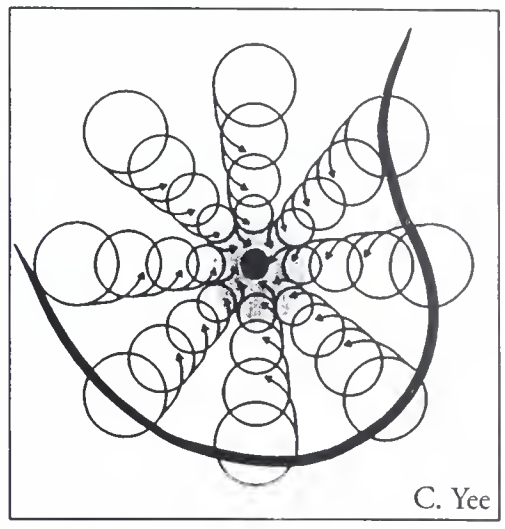
General Considerations

Palpation in the sitting and in the recumbent position is advisable. It is important to realize that normal variations exist in the 'feel' of breast tissue. Breasts of younger patients are more difficult to assess as they are firm and glandular in texture whereas breasts of older patients may be atrophic with a dominant fatty component. The monthly cyclic physiological changes that occur in the breasts will influence their characteristics. Premenstrual fullness, nodularity and tenderness are common. The premenstrual nodularity, which may vary in size from a few millimeters to a few centimeters in diameter, is due to fluid retention and cell swelling. These nodules can easily be mistaken by the patient as pathologic disease and make the examination more difficult. For these reasons the optimal timing for breast examination is a week after menses.

Figure 4: Methods of palpation of the breasts



a) The Vertical Strip Method



b) The Radial Vector Method

When palpating a breast the examiner must be thorough and systematic. Figure 4 illustrates the two methods which are commonly practiced for palpation. With the *Vertical Strip Method*, the breast is palpated systematically along vertical strips, or in an antiparallel vector pattern (Figure 4a). With the *Radial Vector Method*, the palpation begins at the outer edges of the breast moving to the nipple along vectors in a pattern resembling the spokes of a wheel (Figure 4b). Either method is acceptable as long as every part of the breast is examined including the nipples and areolae. The boundaries of palpation are from the 2nd to the 6th rib (bra line) and from the lateral border of the sternum to the midaxillary line (Figure 5).

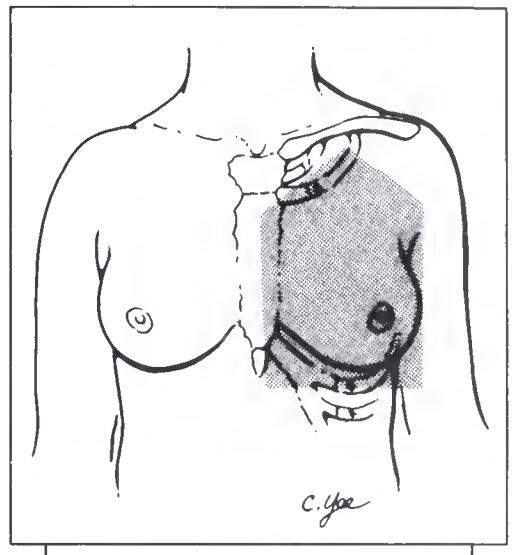


Figure 5: Area to be covered during palpation of the breast

The palpation should be performed methodically with the flat palmar surfaces (pads) of the second third and fourth fingers of the examiner's preferred hand (Figure 6). Small, circular (dime size) movements should be made. Initially, very gentle pressure is exerted evenly over the three fingers. This is followed by medium pressure, then more firm pressure is applied but not to the point where it is discomforting to the patient. The examiner should be thorough and consistent since improper palpation can sometimes create the illusion of a mass.

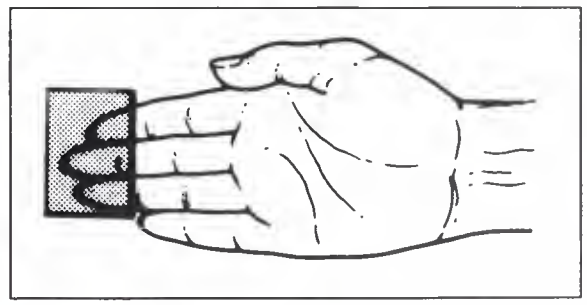


Figure 6: Use of the pads of the three middle fingers is recommended

The patient is first examined in the sitting position with her hands placed behind her head. The patient is then examined in the recumbent position. The following is a description of the palpation of the breasts with the patient in the recumbent position. The same techniques should be applied when examining the patient in the sitting position.

Examination in the Recumbent Position

PALPATION

The Vertical Strip Method

Ask the patient to lie down. If the patient has complained of tenderness or a lump in one of the breasts it is recommended that the opposite breast is palpated first. The lateral aspect of the breast should be examined first. Each breast is palpated carefully and systematically beginning in the axilla with the pads of the three middle fingers (Figure 7). The three levels of pressure should be used as described above. Each set of rotations covers an area of approximately 1 square inch and partially overlaps the previous set of rotations (Figure 4a). The first strip follows the midaxillary line and ends at the bra line of the patient (6th rib). The second strip is anti parallel and overlapping with the first strip. This procedure should be continued until the final vertical strip which runs along the sternum.

Small breasted women may lie in the supine position with their arms at their side. However for large breasts, in order to be able to feel the deeper parts of the breast tissue, it may be helpful to distribute the breast more evenly across the chest wall. This is especially important when examining the lateral areas of the breast. A recommended maneuver is to ask the patient to assume an oblique position while she rests her forearm (on the side that is being examined) on her forehead as shown in Figure 8.

The Radial Vector Method[7]

The patient is examined in the supine position with her hand (on the side that is being examined) placed behind her neck. First examine the medial aspect of the breast systematically covering all vectors. Palpation begins in the 12 o'clock position, just below the clavicle, with small circular movements using the three middle fingers as described above. After reaching the nipple, the procedure is repeated from the periphery along a different but overlapping vector (Figure 4b).

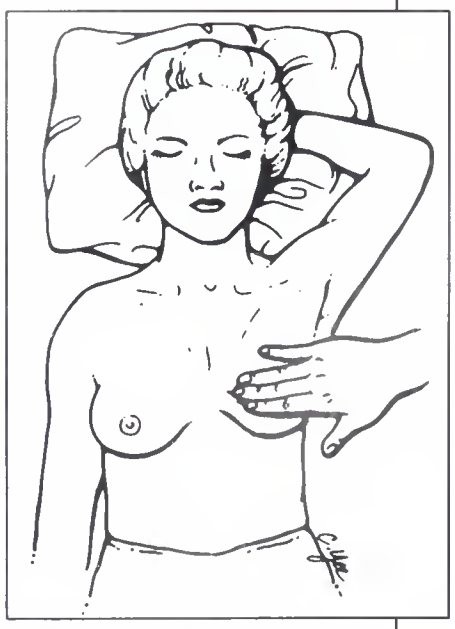


Figure 7: Palpation of the left breast

Figure 8: Patient in the oblique recumbent position

- Size
- Shape (round; regular (smooth)/irregular)
- Consistency (soft/firm/hard)
- Delineation (discrete/blends into surrounding tissue)
- Tenderness
- Mobility

A large proportion of breast tumours in the female are due to fibroadenomas and fibrocystic condition (both of which are benign) and to carcinomas. The characteristics of each of these lesions are presented on Table 4.

Fibroadenomas which were formerly described as a "breast mouse" because of their specific character on physical exam, usually occur in young women in their late teens to early 30s. They are usually discovered at the 1-3cm size and in some patients (10-15%) they are multiple and bilateral.

Fibrocystic condition is a poorly defined term that implies the presence of macroscopic fluid filled cysts in the breast that are usually multiple and of variable size. It is the most common lesion affecting the female breast with increased incidence in women 10-15 years prior to their menopause.[7] Monthly cyclic breast symptoms of pain and lumpiness, especially in the premenstrual or midcycle periods, are common with this condition.

Breast cancer in its early stage is manifested by a solitary, unilateral, hard, painless, poorly-circumscribed lump that invades adjacent tissues. Distinguishing a malignant mass from naturally occurring benign nodules (fibroadenomas or fibrocystic disease) may be difficult. In addition to the specific physical exam findings, other factors such as increasing age and family history of breast cancer will help the examiner determine the need for further investigation. The skill of identifying breast lumps will be attained in due time with enough patience and practice and will be proportional to the enthusiasm and commitment of the examiner.

Table 4

Usual Characteristics of Common Breast Lesions[9]

	Cancer	Fibroadenomas	Fibrocystic condition
Location	unilateral & solitary	unilateral & solitary	multiple & bilateral
Size*	1-3cm	1-3cm	variable
Shape	irregular	round or discoid	irregular, lumpy
Consistency	firm or hard	usually firm & rubbery	glandular
Delineation	often tethered	discrete	blends with tissue
Tenderness	no tenderness	no tenderness	tenderness
Mobility	not freely mobile	extremely mobile	mobile

**usual size at time of discovery*

Palpation of the lateral position of the breast is carried out in a similar fashion. The patient then assumes the oblique position, as in the vertical strip method, in order to allow an even distribution of the breast tissue over the chest wall and the lateral portion of the breast is re-examined.

Description of Breast Masses

The precise location and size of any significant physical findings should be documented on a drawing of the breast that becomes part of the patient's record. A written description of the abnormality should also be noted. If nodules are present their description should include the following:

- Location (quadrant or clock method; distance from nipple)

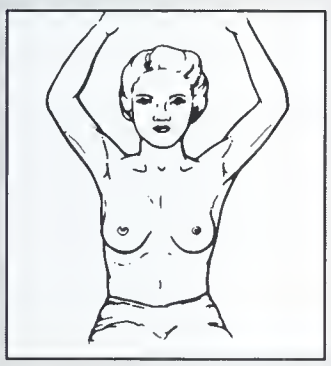
Clinical Breast Examination: A Review

Perform the examination in the following routine order:

1. Inspection

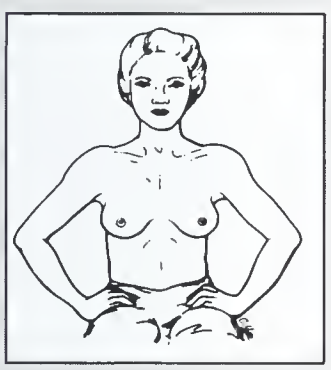
A. Patient Sitting with Hands Resting on Thighs

Inspect each breast



B. Patient Sitting with Arms Raised

Inspect each breast



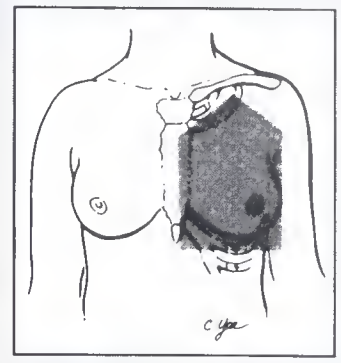
C. Patient Sitting with Hands Pressing Hips

Inspect each breast

D. Patient Sitting and Leaning Forward

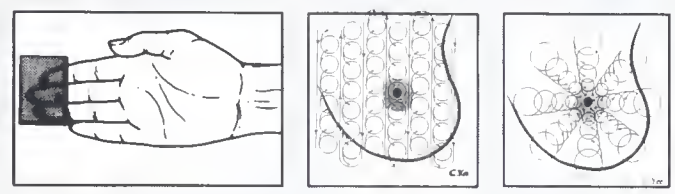
Inspect each breast

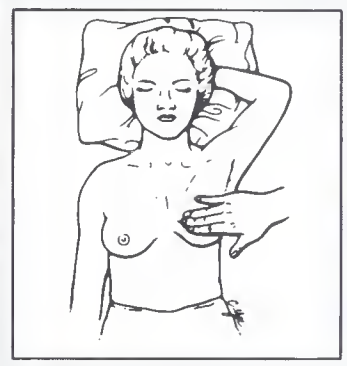
3. Palpation



A. Patient in the Sitting Position

Palpate each breast using either the Vertical Strip Method or the Vector Method





B. Patient in the Supine Position

Palpate each breast using either the Vertical Strip Method or the Vector Method

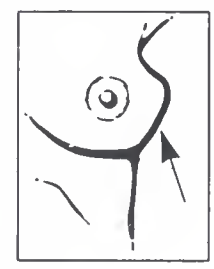
C. Patient in the Oblique Position

Palpate each breast using either the Vertical Strip Method or the Vector Method

Inspect each breast. Note

1. Size and Summetry

2. Change in Contour



3. Superficial Appearance

(e.g. peau d'orange)

(e.g. increased vascularity)

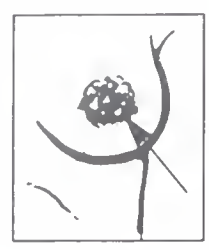
2. Examination of the supraclavicular area and the axillae

While the patient is sitting upright palpate the supra-clavicular area and the mid and upper portions of the axilla

Inspect each nipple. Note

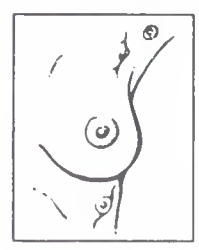
1. Size and Shape

2. Ulcerations or eczema



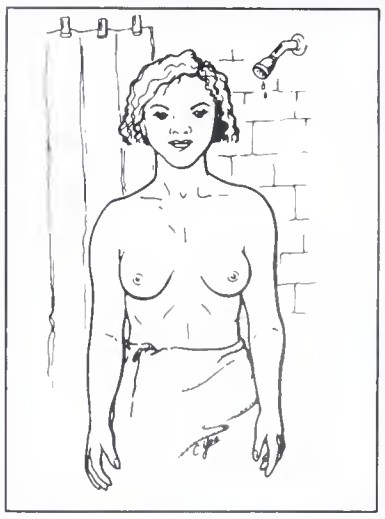
3. Discharge

4. Supernumerary Nipples



*cutaway section

The Breast Self-Examination

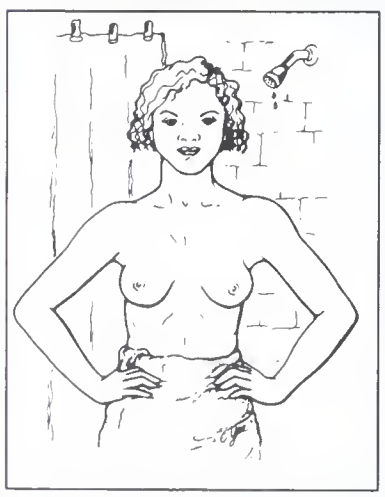


1. Stand before a mirror with your arms relaxed at your sides and observe your breasts carefully.

a) Look for swelling or puckering of the skin
b) Look for changes in size or shape
c) Look for redness or change in texture such as an orange peel appearance
d) Look for changes in the nipple such as indrawing or eczema

2. Lift your arms over your head and look again for the same changes.

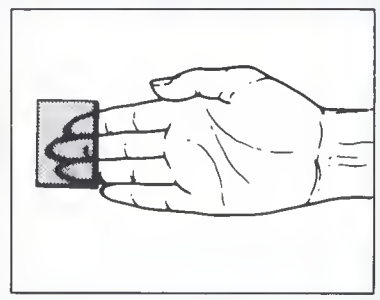
3. If your breasts are large elevate each breast and look in the undersurface for the same changes.



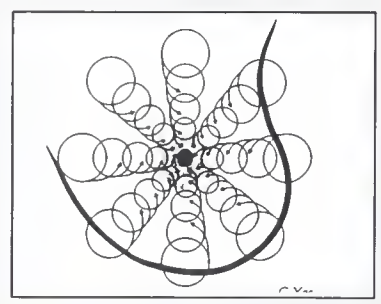
4. Press your hands on your hips to tense your chest and look for the same changes.

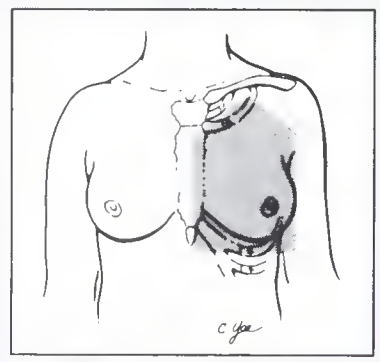
5. Examine your breasts and armpit area by feeling for lumps

6. Lie flat on your bed, raise one arm behind your head and feel your breast with the opposite hand.



7. Use the soft pads of your middle three fingers and with circular overlapping movements (about the size of a dime), feel the breast starting from the outside and moving toward the nipple making a pattern resembling spokes on a wheel. Make sure you press firmly.





8. The area examined is from just below the collarbone to the lower boundary of the breast and from the breast bone to the outside boundary of the breast.

9. Switch hands and examine the other breast.

10. Steps 7-9 should be repeated in the shower. Wet, soapy skin is more sensitive.

*cutaway section

Conclusion

Proper examination of the female breast requires; 1. evaluation by history taking; 2. a thorough and careful physical examination of the breast, the supraclavicular area and the axillary lymph nodes and; 3. knowledge of the signs and symptoms of benign and malignant conditions. A suspicious finding on examination should always be worked up appropriately. By following the procedures outlined in this paper, including educating women on the proper techniques of performing a breast self-examination, the health provider will be contributing to reducing the mortality and morbidity which are associated with breast cancer.

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The Magnetic Resonance Imaging Appearance of Hypertrophic Olivary Degeneration After a Unilateral Tegmental Hemorrhage; Evidence for an Anatomical Connecting Pathway in the Myoclonic Triangle

Eric J. Versnick (9T6) and David J. Mikulis, MD, FRCP(C)*

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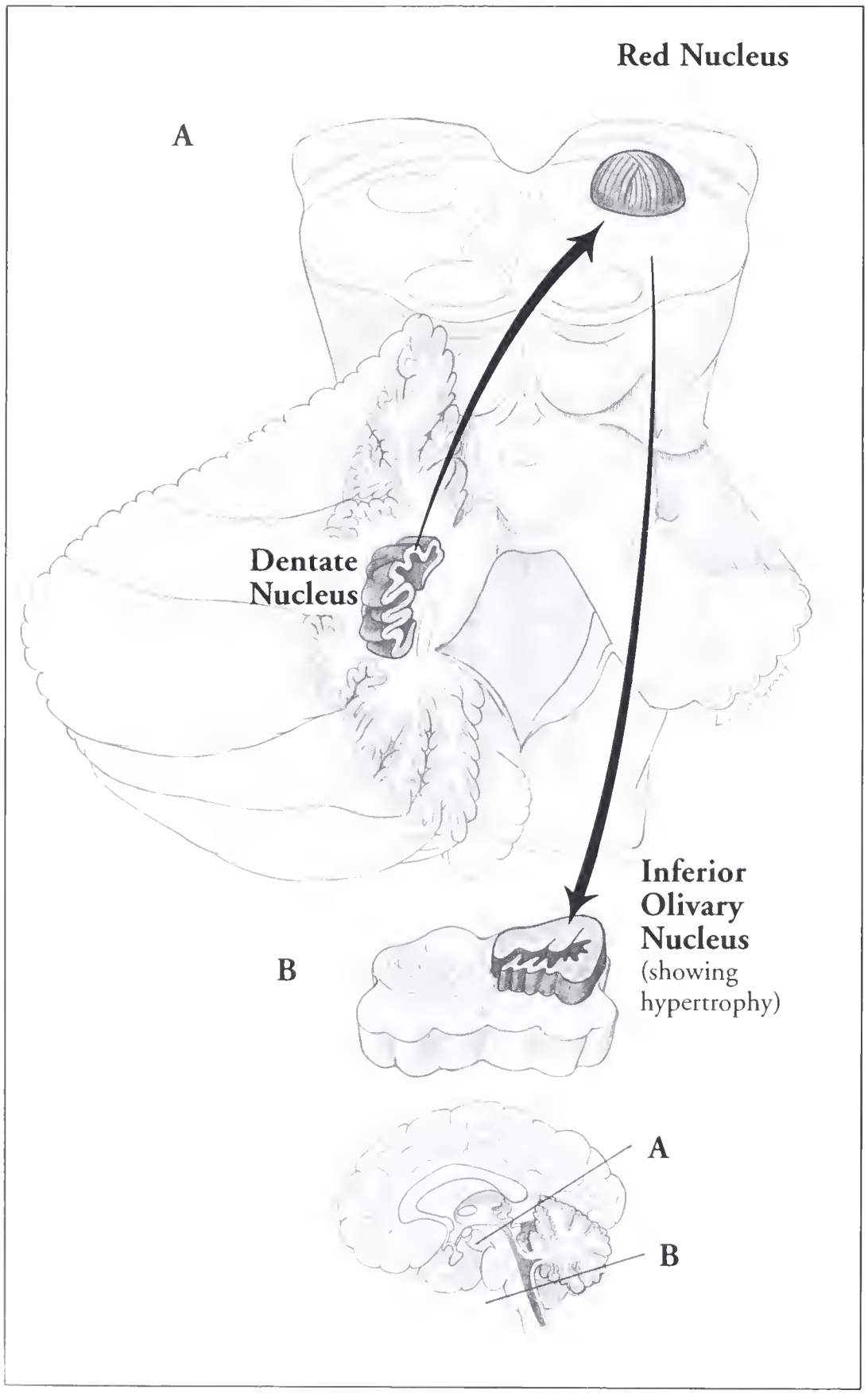

LORETTA deGROOT

Abstract

Hypertrophic olivary degeneration of the inferior olivary nuclei (ION) is a time delayed response that occurs subsequent to a lesion in the myoclonic triangle, a specific set of afferents leading to the inferior olivary nucleus. The magnetic resonance imaging (MRI) reports in the literature typically show hypertrophy and increased signal of the olives on T2 weighted and on proton density imaging. With time there is resolution of the hypertrophy but increased signal persists. We present a case of a forty-one year old male who developed a hemorrhage into the right side of the tegmentum in the midbrain and the upper pons. Serial MRI showed bilateral hypertrophy and increased signal on T2 weighted imaging without subsequent resolution of hypertrophy. The bilateral changes in the olivary nuclei subsequent to a unilateral lesion does not reflect currently accepted neuroanatomy of the myoclonic triangle. This evidence suggests the presence of connecting pathways between the right and left tegmental pathways.

Introduction

Hypertrophic olivary degeneration is a rare and fascinating condition affecting the olivary nucleus in the ventral medulla of the brainstem. Clinically, hypertrophic olivary degeneration is associated with palatal myoclonus, a condition in which there is superior and posterior movement of the soft palate. Usually, palatal myoclonus does not interfere with swallowing or breathing and is only detected on examination[1]. Occasionally, the patient may complain of

Figure 1: A T1 weighted axial image through the upper pons three months after the hemorrhage. Arrow points to the site of the hemorrhage

Figure 2: A proton density axial image through the level of the medulla eight months after the hemorrhage. Arrows point to the hypertrophic olivary nuclei which also show increased bilateral signal

a clicking noise, the suggested cause of which is the opening and closing of the Eustachian tube by the tensor veli palantini. Rates of the myoclonus average 100-150 per minute and most often, the condition continues for the remainder of the patient's life[2].

MRI investigators have reported hypertrophy and increased signal in the ION as hallmarks of this condition[3, 4, 5]. Historically, this condition was discovered when post mortem studies of the brainstems of patients with palatal myoclonus revealed hypertrophic changes in the ION. Recently, pathologists have demonstrated enlarged inferior olivary nuclei with vacuolation of neurons, an increase in the number of glial cells, demyelination and shrunken neurons[6, 7, 8, 9].

It has been postulated that any lesion within a specific set of supraolivary tracts named the myoclonic triangle, results in transsynaptic degeneration with a time delayed hypertrophic ION changes. The tracts were first described by Guillain and Morraret[10, 11] and were proposed to run from the dentate to the contralateral red nucleus and then to the olivary nucleus. The triangle was completed when the olivary nucleus was found to connect directly to the contralateral dentate by the inferior cerebellar peduncle. A neuroanatomist named Trelles was lead to describe the currently accepted pathway because palatal myoclonus was never observed with lesions of the inferior cerebellar peduncle [10,11]. Trelles' pathway runs from the contralateral dentate nucleus to the adjacent superior cerebellar peduncle and then crosses to the ipsilateral side to run along the dorsal surface of the red nucleus. From here the pathway continues in the central tegmental tract to end in the inferior olivary nuclei. This pathway was confirmed in the cat by using autoradiographic tracing[12]. For historical reasons, the pathway is still commonly referred to as the Guillain and Morraret triangle.

History

A forty-one year old previously healthy gentleman experienced sudden onset of headache, left sided weakness, and blurred vision upon awakening in the morning. There was no associated loss of consciousness, seizure activity, nausea or vomiting.

Figure 3: A T2 weighted axial image at the level of the medulla eight months after the hemorrhage. Arrows point to the hypertrophic olivary nuclei which also show increased bilateral signal (signal greater in the right olive)

Examination

On examination, the patient's vital signs were normal. He was oriented to person, place and time. His speech was dysarthric. Eye examination revealed small reactive pupils with impairment of upgaze, a fine gaze evoked vertical nystagmus and incomplete abduction of the right eye. Fundoscopy was normal. The gag reflex was slightly decreased and palatal myoclonus was absent. A mild left facial palsy was present. The rest of the cranial nerves were normal. Motor testing showed slight impairment on the left side with strength graded at 4/5. There was left sided body and face hypesthesia to pinprick and light touch and absent left sided proprioception. Right sided cerebellar signs of finger to nose incoordination, heel to shin incoordination and adiadochokinesia were present.

Investigation

Computerised tomography (CT) of the head on presentation showed a 1.5cm hematoma in the right side of the tegmentum in the midbrain extending down to the upper pons. Angiography, performed to determine the cause of the acute bleed was normal. MRI on day eight clearly defined the hematoma and also showed adjacent vascular flow voids suggestive of a developmental venous anomaly. No abnormalities were seen in the inferior olivary nuclei. Followup MRI was performed at three and eight months. The three month MRI showed evidence of the old hemorrhage (Figure 1) and hypertrophy of the left inferior olivary nucleus with increased signal in the left olive on T2 weighted and proton density images. Proton density images (Figure 2) and T2 weighted images (Figure 3) at eight months demonstrated bilateral hypertrophy and increased signal with the signal greater in the right olive. These MRI studies suggested the presence of a tegmental cavernous angioma as the source of this patient's hemorrhage.

Discussion

Lesions caused by infarcts[13,14], hemorrhages[3,4,15,16], syphilis[1,17], neoplasms[1,18], and trauma[1,3,4,18,19] have been identified in the myoclonic triangle. In cases where palatal myoclonus is a clinical feature, it has been found that the onset of this movement anomaly is delayed on average by ten to eleven months after the causative lesion has occurred in the myoclonal triangle[20]. This may be related to the duration of the biochemical changes that occur with denervation supersensitivity[20] while others feel that the process is of transneuronal degeneration[7]. This time delay explains why our patient had not developed palatal myoclonus. MRI has also shown peculiarities on serial imaging. Again, it seems that time is required for the olivary changes to evolve after the onset of the initial lesion in the myoclonic triangle.

Birbamer[3] hypothesized three stages to hypertrophic olivary degeneration. Acutely, there is no change in the inferior olivary nuclei, then there is hypertrophy and increased signal, followed by disappearance of the hypertrophy and maintenance of the increased signal[3]. The findings in this disorder of increased signal on T2 and proton density images are in keeping with the pathological processes since gliosis, and increased water content associated with demyelination and vacuolation gives an increased signal[3,21].

The MRI images in our case do not support Birbamer's observation of decreased hypertrophy and maintenance of signal. As well, our observation of a unilateral lesion giving rise to bilateral olivary changes is not consistent with Birbamer's findings or the findings of fourteen other reports of unilateral lesions in the MRI literature[4,5,15,22,23]. Only one other case of a unilateral lesion leading to bilateral olivary changes has been reported[23]. This case reported by Uchino demonstrates a unilateral lesion in the myoclonic triangle resulting from damage to the right cerebral artery during a craniotomy. Uchino did not comment on the anatomic relevence or the uniqueness of this finding.

Birbamer's case is an excellent example illustrating the application of neuroanatomy since the location of the causative lesion determines which olive undergoes change. Birbamer's observation was based on a patient with a hematoma located in the right dentate nucleus. Images at eleven and seventeen months showed hypertrophy with increased signal, and decreasing hypertrophy with maintenance of signal in the contralateral (left) olive respectively[3]. In our case, there was a right-sided tegmental lesion. From our knowledge of anatomy, the change should have occurred in the olive that was connected by the disrupted pathway, for example, the right olive only. Our observation of bilateral changes suggests the possibility of a connection between the right and left pathways in the tegmentum. The fact that we did not observe decreased hypertrophy does not refute Birbamer's hypothesis because the timing of the changes may be variable. It is only with future serial MRI that we may confirm Birbamer's hypothesis.

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Infectious Diseases Rounds

Danyal Ibrahim, MSc (9T7)

The winners of the *UTMJ Quick Diagnosis Competition,* Emergency Medicine Rounds (Vol. 72, No. 2, March 1995) are Barry Chow (9T7) and Hari Mallidi (9T7).

The Journal will be offering a prize of **$50** to the reader who submits the correct diagnoses for all the cases. Responses should be sent to the following address no later than **July 1st, 1995.**

Quick Diagnosis Competition
c/o Danyal Ibrahim - Quick Diagnosis Editor
University of Toronto Medical Journal, Room 2141, Medical Sciences Building, Toronto, Ontario M5S 1A8

Case 1

Andrew E. Simor, MD, FRCP(C)

Figure 1: Photograph of right forearm showing the skin lesions.

Clinical History

A 47-year-old woman presented with a 4-week history of progressive nodular skin lesions on her right forearm. She has had no fever or chills, and is otherwise in good health. She is on no medications. She is a married woman, with two children, and she works part-time in a florist's shop. Physical findings are shown in Figure 1.

What is the most likely diagnosis?

Dr. Simor is an Associate Professor in the Department of Microbiology and Division of Infectious Diseases, Sunnybrook Health Science Centre.

Case 2

Ellen Warner, MD, FRCP(C), FACP

Figure 1: Photograph of chest wall: *anterior view.*

Figure 2: Photograph of chest wall: *lateral view.*

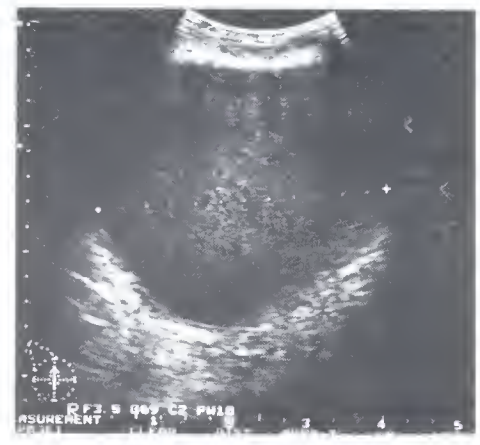

Figure 3: Ultrasound of right chest wall showing 12 x 6 x 9cm echo-poor area.

Clinical History

This 62-year-old lady had a right modified radical mastectomy for a poorly differentiated infiltrating duct carcinoma. Tumour was found in 6 of 10 axillary lymph nodes. Several weeks post-operatively a large chest wall seroma was aspirated. She received combination chemotherapy for 6 months followed by radiation to the chest wall and regional lymphatics. Four months later she presented with a 1 month history of partial regrowth of her right breast including the nipple. She admitted to increasing fatigue, with fever and chills in the late afternoon.

On examination, there was a huge fluctuant mass under the mastectomy scar. The overlying skin was dusky red with peau d'orange (Figure 1 and 2). In one area the skin was markedly thinned and redder. Ultrasound is shown (Figure 3).

What is the most likely diagnosis?

Dr. Warner is an Assistant Professor in the Department of Medicine, Division of Medical Oncology, Sunnybrook Health Science Centre.

Case 3

Anita R. Rachlis, MD, FRCP(C), MEd

Clinical History

A 40-year-old gentleman from South America presented with 4 week history of fever, fatigue, weight loss, and mild cough.

A chest x-ray revealed reticulo-nodular pattern.

A generalized papular skin rash was noted on examination (Figure 1). A biopsy of the skin rash was carried out (Figure 2).

Figure 1: A photograph of the skin rash.

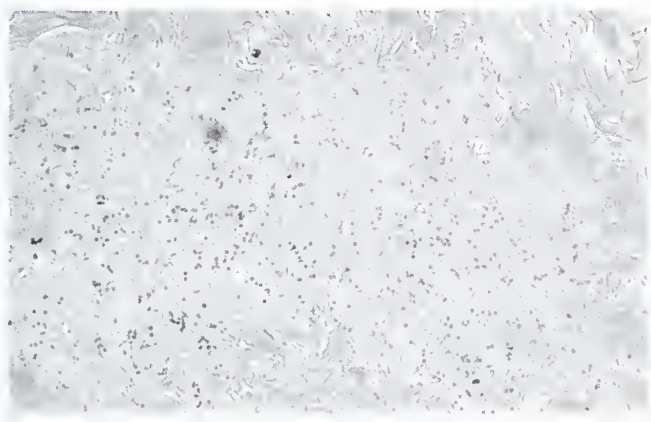

Figure 2: Silver stain of the skin rash biopsy.

What is the most likely diagnosis?

What may be a predisposing condition in this case?

Dr. Rachlis is an Associate Professor in the Department of Medicine, Division of Infectious Diseases, Sunnybrook Health Science Centre.

ANSWERS TO QUICK DIAGNOSIS: *(UTMJ Volume 72, Number 2, March 1995)*
Emergency Medicine Rounds

Case 1

Dx. **Disseminated Gonococcal Infection.** Patients typically present with signs and symptoms of gonococcemia. The onset of gonococcemia is characterized by fever, polyarthralgias, and papular, pustular, haemorrhagic or necrotic skin lesions, usually on the distal extermities.

Case 2

Dx. **Tension Pneumothorax.** The emergency treatment requires the insertion of a large bore needle, 2nd intercostal space, med-clavicular line, followed by chest tube, 5th intercostal space, anterior axillary line.

Case 3

Dx. **Leaky Abdominal Aortic Aneurysm.** The plain abdominal x-ray reveals calcification of the aneurysm wall. In the unstable patient, cross-sectional ultrasonography is the most cost-effective noninvasive method of evaluation. CT scanning is even more accurate and may be indicated in the stable patient.

Case 4

Dx. **Hyperkalemia Secondary to Renal Failure.** Electrocardiographic changes start with peaked T waves, then prolongation of PQ, QT and AV intervals, diminished P waves and depressed ST segments. At higher levels P waves disappear, QRS complexes winde, S and T waves merge and ventricular rythyms become irregular.

Case 5

Dx. **Adult Epiglottitis.** Adult epiglottitis appears to differ in many ways from that which occurs in children. The adult disease may not be caused by *H. influenzae* type B, is often not rapidly progressive, and may not be associated with airway compromise.

Case 6

Dx. **Hangman's fracture (fracture of posterior elements of C2).** This fracture is usually a hyperextension injury associated with abrupt deceleration as in high speed MVA.

Case 7

Dx. **Wide mediastinum (suspicious for traumatic aortic disruption).** The x-ray shows a very wide mediastinum, an associated left apical cap, deviation of the NG tube to the right and obliteration of the left heart border between the aortic knob and the left pulmonary artery.

Case 8

Dx. **Metaphyseal Corner Fractures of the Femur (Child Abuse).** These fractures are almost pathognomonic of child abuse and occur secondary to a twisting or shearing force being applied to infants extermities causing a fracture through bony metaphysis into the epiphysis.

Case 9

Dx. **Retropharyngeal Abscess.** This child's x-ray shows marked soft tissue swelling in the retropharyngeal space anteriorly which is secondary to a large abscess, notice the central lucency in this case.

Case 10

Dx. **Pancoast's Tumour.** Pancost's syndrome is a rare, but well described presentation of lung cancer which results from direct apical tumour invasion into the lower portions of the brachial plexus.

Case 11

Dx. **Delayed Non-union of Scaphoid Fracture with Avascular Necrosis.** This is a good example of the complications that can occur with scaphoid fractures.

The University of Toronto Medical School Academies: A Few Good Reasons

Shane Burch, MSc (9T8)

At the start of the 1994-95 academic year, four academies were incorporated into the medical school. At that time, students felt uncertain of the purpose of the academies and the effects that they would have on their education. Almost eight months later, these doubts remain unresolved. This brief report reflects the views of the academy directors, who describe the positive and negative attributes of the academies, why there are four academies, and the reasoning behind their inception.

The four academies include the following: the Boyd (Sunnybrook Hospital), Fitzgerald (St. Michael's and Wellesley Hospitals), the Peters (Mount Sinai and Women's College Hospitals), and the Wightman (Toronto Hospital - General and Western Divisions). Each academy utilizes two teaching hospitals with the exception of the Boyd academy, which has integrated somewhat with the Toronto East General Hospital. Each academy was given its own director, offices, staff and mandate. In September, first and second year students were randomly selected to fill each roster. The academies were designed to facilitate the new curriculum, to provide better communication between hospitals, the community and the faculty of medicine and ensure a uniform education.

The new curriculum in Years I and II entails traditional medical courses such as anatomy, biochemistry, and physiology, but also focuses on the physician's role both in the community and in a clinical team. Teaching the concept of how the physician interacts in the community is dealt with in the Health and Illness in the Community (HIC) course, while the clinical training in Years I and II are taught in the Arts and Sciences of Clinical Medicine course (ASCM). The HIC curriculum allows students to experience community health services such as homecare, community health centres, and drug rehabilitation centres. Both HIC and ASCM occupy a significant part of the new curriculum and both are based in the hospital. The HIC course benefits from being based in the hospital by utilizing the established contacts hospitals have with community health services. As a result the teaching of the new curriculum is somewhat decentralized from the traditional medical sciences building (MSB) location to the hospitals and the community. To help coordinate the decentralized curriculum more direct communication between the hospitals, the community and the MSB have been established with the infrastructure of the academies facilitating this process.

The second advantage of the academies is as follows. The Toronto teaching hospitals are under pressure to specialize: in the future, comprehensive standard services will not be available at every hospital. Therefore, clerks, who were traditionally stationed at one hospital, now transfer between hospitals in order to meet their requirements and interests. Furthermore, as hospitals specialize, standards required to maintain equality in education are jeopardised. For example, facilities and services provided by the hospitals, available teaching staff, and community contacts - all of which have effects on the thoroughness of education - may differ significantly. By amalgamating Toronto's teaching hospitals into academies, teaching resources can be integrated and disparities can be reduced. It should be added that, in view of the pressure to decrease the number of teaching hospitals in the Toronto area, allocating six teaching hospitals to four teaching academies is politically shrewd.

However, as the hospitals specialize the academies will also tend to specialize, and because of this, the academies are regulated to insure that uniform undergraduate education is being maintained. To this end, the academy directors meet once a month with the Dean of Undergraduate Medicine to discuss operational problems and to equalize services. Issues discussed relate to the coordination of staff teaching physicians, sequestering space for teaching, and to lesser issues such as equalizing the number of free photocopies available to students. The academy directors are also the direct facilitators of the communication between the community, the hospital and the MSB.

To some degree the directors also foresee the academies helping students integrate into the medical school socially. One way of accomplishing this is to promote social events within each academy involving Years I through IV. This would encourage vertical integration in the academy. Harvard medical school, which is equal in size to U of T's medical school also operates with academies. The academies at Harvard, however, have a strong social tradition. Unfortunately, the benefits of segregated social societies leading to fellowship in Canadian universities

are almost unknown. Yet the obvious funding potential of this approach suggests that substantial benefits may result. If, for example, social competition were to develop between the academies, integration of all four Years of the medical school may be initiated. Whether a sense of fellowship and affiliation would result depends on the students.

The new system may face difficulties if the academy directors fail to meet their goal of education equality. Furthermore, as the academies strive for their identities, precautions must be taken to inhibit this from happening academically. The academies are fledgling and have been established at a time when the provincial government is faced with reduced transfer payments. If one of the teaching hospitals in Toronto loses its status, the academies will most certainly change. The academies have cost both the medical school and the hospitals money to develop. Whether this unique approach will benefit medical education is yet to be determined.

However, the academies are currently politically favourable, academically advantageous and necessary for a uniform education. For the students, the academies have opened an enormous opportunity to integrate the medical school. This is an opportunity students should embrace with enthusiasm.

Sincere thanks to the academy directors and to Dean Frecker for their helpful insight.

Care to be part of the solution?

The medical education system is adapting to the changing needs of society to ensure that tomorrow's doctors are equipped to meet tomorrow's challenges.

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BOOK REVIEWS

Ambulatory Medicine

by Mark B. Mengel and L. Peter Schwiebert, editors.
Appleton & Lange, 1993. 647 pp.
Cost: $34

When confronted with the task of selecting the "perfect" clinical reference manual, one must consider a number of factors. Ideally, the manual should be informative, easy to read, portable and affordable. *Ambulatory Medicine,* another member of the Lange family of medical texts and manuals, attempts to satisfy these criteria.

Primarily intended for medical students and residents, this reference companion includes information relating to the sixty-six most common health-related complaints as reported in surveys of family medicine, internal medicine and paediatric clinics. Because topics are arranged alphabetically, specific complaints can be addressed without knowing which disease process is involved. This is especially useful to the medical student who is learning to interpret clinical findings.

Each complaint is introduced by a definition, followed by sections covering common diagnoses, epidemiology, pathophysiology, signs and symptoms, laboratory investigations, treatment and a list of current references. Interspersed within the text are tables, figures and flow charts.

Topics are well organized and explain concepts without confusing the reader with jargon. Avoidance of fine details allows the reader to gain a better understanding of the general concepts without getting overwhelmed by minutia. The figures, flow charts and tables nicely supplement the text, summarize key concepts and provide the reader with a systematic approach to addressing complaints in a clinical environment.

For the most part, this is an excellent manual. However, certain areas would benefit from more figures. This is especially true in the physical examination sections of various joint pains. Of lesser concern, the references provided for topics such as chest pain are not the most current.

In *Ambulatory Medicine:* The Primary Care of Families, the editors have succeeded in producing a concise reference companion that includes most of the pertinent information relating to some of the more common complaints encountered in medical practise. Its strengths far outweigh its shortcomings and should be considered by the medical student or resident interested in purchasing a general clinical companion.

Joy Banerjee (9T7)

A Little Book of Doctor's Rules

Clifton K. Meador. Philadelphia, Hanley & Belfus, 1992.
Cost: $14.25

"Oh no! Not another quaint little book of trite phrases containing trivial wisdom!" was what I thought when I first saw A Little Book of Doctor's Rules. If you've ever been to the Psychology section of any bookstore and seen the other books of this 4x6" pocket-sized book genre, such as *Life's Little Instruction Book* (Volumes 1 and 2), *Live and Learn and Pass it On, etc., etc., ad infinitum,* you know what I mean.

However, curiosity got the better of me, and I picked it up (with a slight snort of derision) and flipped through it. Now it is on my shelf along side my other source of conventional wisdom (*Life's Little Instruction Book* — it was a gift, okay?). Call me silly. Call me naive. But I liked the book.

Written by Clifton K. Meador, M.D., *Doctor's Rules* begins with a preface explaining his motivations for writing such a book. In his training, he searched for an all encompassing set of rules to guide him in the practice of medicine. He found that the works of Hippocrates and Osler were decidedly outdated. Instead, he compiled his personal notes and input from his colleagues.

The result is 425 entries of conventional wisdom. They range from prudence when prescribing medication to politeness in an office. What struck me the most was the humility with which Dr. Meador made his entries. With full appreciation of the power a physician holds in a doctor-patient relationship, he tempers the relationship with compassion and kindness.

I found *Doctor's Rules* a fascinating set of suggestions on personal and professional conduct — ASCM from a different point of view. It can be very useful to point out some important ideas that are easy to forget while practicing medicine, not to mention a pleasure to read.

Sandy Dong (9T7)

Heitzman's The Lung: Radiologic-Pathologic Correlations (3rd ed.)

by Stuart A. Groskin, M.D., St. Louis, Mo., Mosby-Year Book, Inc. 1993.
Cost: $95 U.S.

In basic terms, *Heitzman's The Lung: Radiologic-Pathologic Correlations, 3rd ed.* describes exactly what is stated in the title. For a whole host of respiratory disorders, it concentrates on showing the reader what might be seen a) histologically in such affected tissue, b) grossly, in a pathological specimen and c) on an x-ray of a patient afflicted with that particular disease. Hence, the authors have tried to bring together related information from histology, pathology and radiology atlases and textbooks into a single "one-stop shopping" textbook. Does it succeed in this objective? Read on.

Because radiology, and to a lesser extent histology, are such visually-oriented disciplines, one would expect that any textbook that tries to link the two would be full of illustrations, diagrams, pictures, etc. In this regard, *Heitzman's The Lung: Radiologic-Pathologic Correlations, 3rd ed.* doesn't disappoint. For a 636 page book, it boasts 857 illustrations; you do the math: that's over a picture a page. The reader can be assured that for any given illness, there's a photo of a relevant x-ray somewhere in the textbook. Finally, after all this talk about "bulli", "Kerly-B lines", etc. there's a place to turn when one wants to know what they really look like on an x-ray, and what causes them. The textbook covers such topics as pulmonary embolism, pulmonary edema, neoplasms, atelectasis and chronic obstructive pulmonary disease, as well as less common diseases related to the pleura, etc. In addition, 120 of the 636 pages are devoted to a discussion of chronic interstitial lung diseases (which is very useful if, after having taken a week of respiratory medicine, one is still uncertain about the difference between pneumoconiosis, silicosis, asbestosis, etc.). Each chapter includes a discussion of the etiologies, pathologies and pathophysiologies of the various diseases and disease processes. As well, a strength of this book is the willingness of the authors to define some often confusing nomenclature, ensuring that they and the readers are on level playing fields. Novices, particularly first or second year medical students, often become confused when words such as "panacinar, panlobular, etc." are spread about by clinicians and others who assume that they already know what these words mean. Thus, the textbook is very accessible to beginners in this regard.

It must be re-emphasized that the scope of this book does not include a description of the nitty-gritty of every disease process. If it did, the book would be suitable as a training tool for a highly ranked shotput team. Instead, the text spares the reader any unnecessary detail and gives him/her the "fast food" of the material. However, once in a while the "fast food" is not enough, and the reader is left hungry for more: "why does this happen? what is the effect of this on that? what are the molecular genetics as applied to alpha-1 antitrypsin deficiency, and how are RFLPs and VNTRs used to study them?" Does the author leave the faithful reader out in the cold? Not at all; each chapter is supplemented with more than enough references to guide the reader towards the desired information. The reader can seek out as much or as little extra information as required, but is always supplied with enough information to speak fairly confidently in the toughest PBL group. However, this does not imply that the textbook is of too elementary a nature to be useful for clinical clerks or residents: the quality and great diversity of the illustrations and photos (particularly the clinical x-rays) makes the book useful in most clinical settings.

Two chapters stand out as being especially useful in *Heitzman's The Lung: Radiologic-Pathologic Correlations, 3rd ed.* The first is chapter four, entitled "Subsegmental anatomy of the lung". This is the chapter where the normal anatomy of the lung is reviewed, from the bronchi down to the alveoli, including the lung parenchyma. The textual review is highlighted by some outstanding x-rays including normal films and barium venography. As well, suitably cross-sectioned gross sections and some slick (though reprinted by permission of CIBA and Frank Netter) illustrations are included to facilitate the discussion. Again, useful background information is presented without the need to scurry around for basic textbooks. Another very useful chapter is chapter five, entitled "Pattern recognition in pulmonary radiology." This is the chapter that provides sweet salvation to the reader who regards such terminology as "disseminated alveolar appearance, pseudoalveolar appearance and disseminated interstitial or nodular disease" as igpay atinlay. It describes and illustrates, through the use of excellent x-ray photos, the difference between reticular patterns, nodular patterns and everything-in-between (reticulonodular patterns??). Furthermore, the chapter provides a nice summary of what diseases might produce such patterns (i.e. why they occur). Of course, many of these diseases are discussed at greater length later in the book, but this is a good synopsis.

The major difference between the third edition of this textbook (published in 1993) and the second edition (published in 1984) is a chapter outlining the pulmonary manifestations of AIDS. The book really excels in its coverage of the causes (be they infectious, neoplastic, miscellaneous) of respiratory pathology in AIDS, and provides x-ray photos of most of them. The book provides some useful epidemiological and etiological information, but certainly does not replace a textbook of

infectious disease/microbiology. It does, however, offer by numbers the largest selection of references (305) of any chapter. Unfortunately, several of them seem outdated.

Many good qualities of this textbook have been outlined above, but life is not all peaches and cream. There are a few shortcomings to the book. While the x-rays and gross sections of photos make it relatively easy to see what's going on, the histological sections are often not at a high enough magnification for the reader to discern what is being indicated/emphasized by the arrows. The fact that the histological pictures are in black and white (as opposed to the more familiar and soothing pink and blue) compounds the problem. This leads into another issue, that of there being no colour whatsoever in the book, which makes the book somewhat bland to look at (thank goodness for all those pictures). A final nit-picky problem is that often the reader has to flip around quite a bit to find the text that corresponds to the various figures, which can be somewhat distracting. Fortunately, each diagram does have a sufficiently detailed caption to tide the reader over.

In summary, *Heitzman's The Lung: Radiologic-Pathologic Correlations, 3rd ed.* is a very useful (yet accessible to most levels of training) textbook that, all things considered, give a lot of bang for the buck.

Robert Masnyk, BSc, (9T7)

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Robbins Pathologic Basis of Disease (5th edition) *Cotran, Kumar and Robbins, editors* *W.B. Saunders Company, 1994* *Reviewed by Hari Mallidi (9T7) and Barry Chow (9T7)*	43

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Reinders FX, Chalin C, and Meier HMR. Alzheimer's disease: Understanding the patient and caregiver. UTMJ 1993; 70(2): 16-20.

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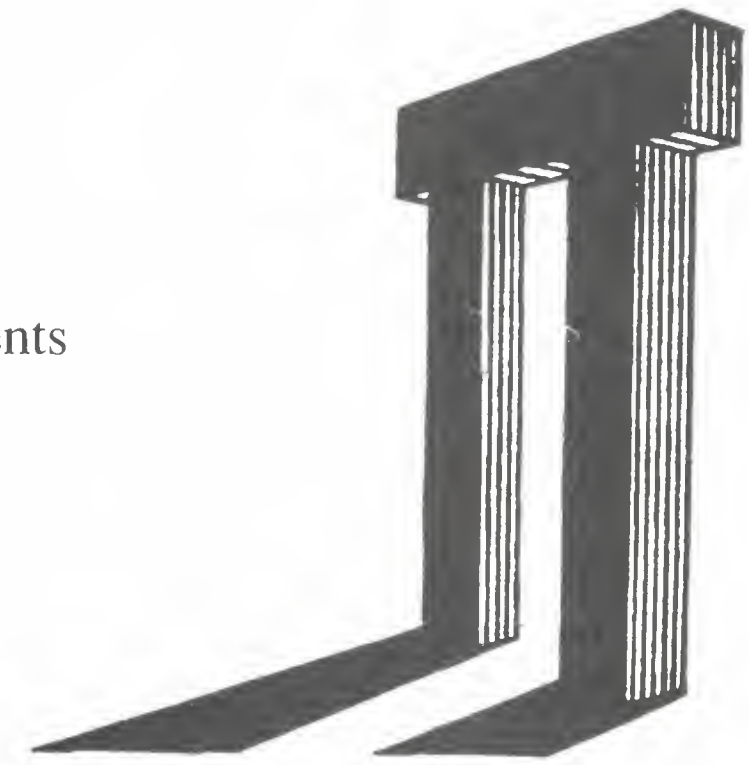

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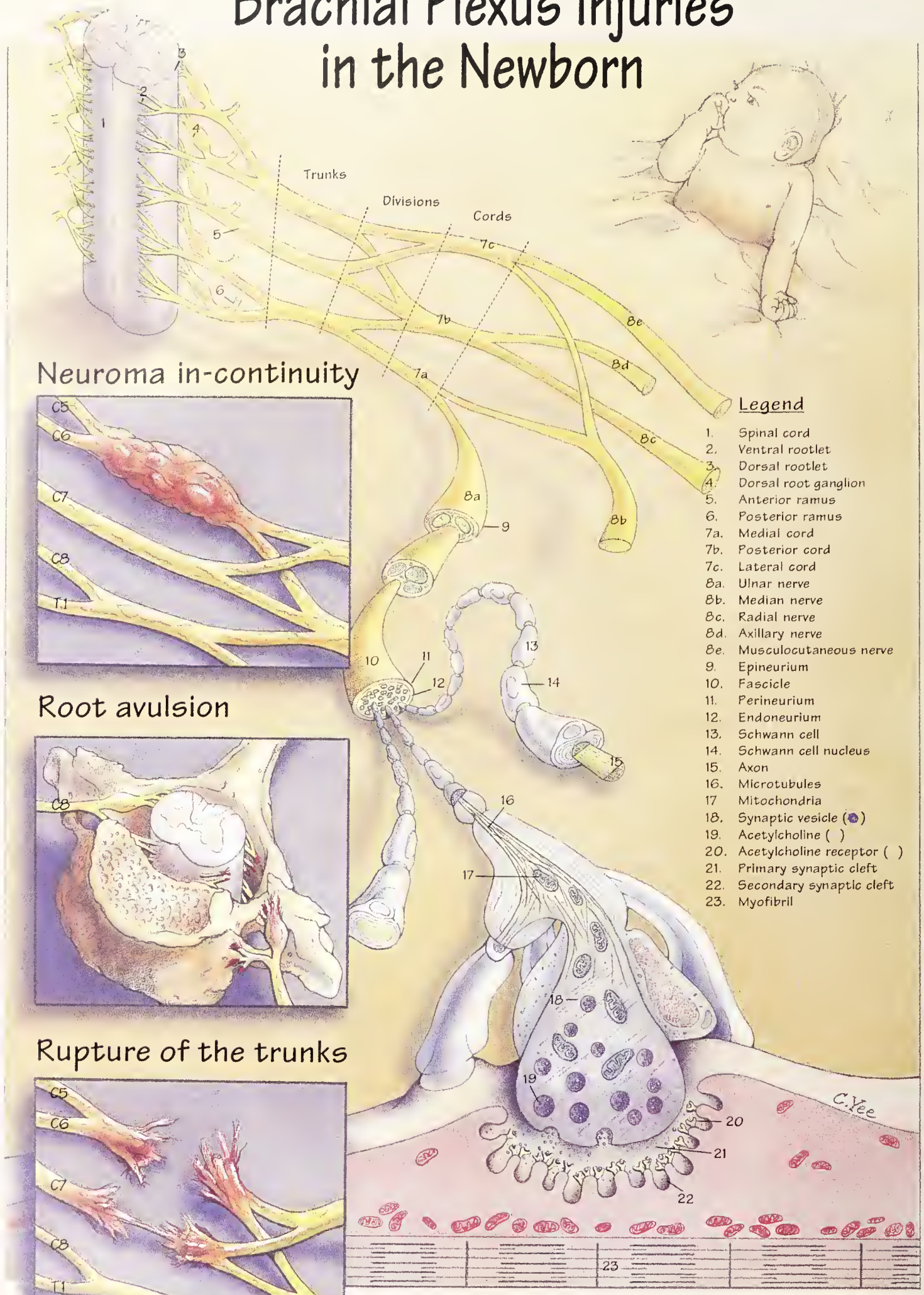

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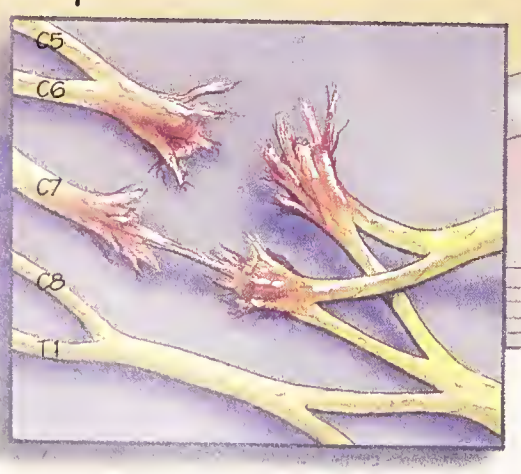

Legend

1. Spinal cord
2. Ventral rootlet
3. Dorsal rootlet
4. Dorsal root ganglion
5. Anterior ramus
6. Posterior ramus
7a. Medial cord
7b. Posterior cord
7c. Lateral cord
8a. Ulnar nerve
8b. Median nerve
8c. Radial nerve
8d. Axillary nerve
8e. Musculocutaneous nerve
9. Epineurium
10. Fascicle
11. Perineurium
12. Endoneurium
13. Schwann cell
14. Schwann cell nucleus
15. Axon
16. Microtubules
17 Mitochondria
18. Synaptic vesicle ( )
19. Acetylcholine ( )
20. Acetylcholine receptor ( )
21. Primary synaptic cleft
22. Secondary synaptic cleft
23. Myofibril

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